

FORM PTO-1390
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Attorney's Docket Number

**TRANSMITTAL LETTER OF THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)**

81823/20860

09/555575

International Application No
PCT/SE99/01075

International Filing Date
16 June 1999

Priority Dates Claimed
22 June 1998

Title of Invention
Novel Compounds Useful in Pain Management

Applicant(s) for DO/EO/US
Daniel Delorme, Vlad Gregor, Edward Roberts, Eric Sun

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items under 35 U.S.C. 371:

1. This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).
2. The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees as follows:

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CLAIMS	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
TOTAL CLAIMS		29-20 =	9	9 X \$18.00	\$ 162.00
INDEPENDENT CLAIMS		6-3 =	3	3 X \$78.00	234.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ \$260.00	260.00
Basic National Fee (37 CFR 1.492(a)(1)-(5)):					
<input type="checkbox"/>	For filing with EPO or JPO search report (37 CFR 1.492(a)(5))			\$840.00	
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482)			\$670.00	
<input type="checkbox"/>	No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))			\$690.00	
<input checked="" type="checkbox"/>	Neither international preliminary examination fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO			\$970.00	970.00
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Articles 33(2)-33(4)			\$96.00	
Surcharge of \$130.00 for furnishing the National fee or oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).					
TOTAL OF ABOVE CALCULATIONS					= 1,626.00
Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (Note 37 CFR 1.9, 1.27, 1.28).					
SUBTOTAL					+ 1,626.00
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).					
TOTAL NATIONAL FEE					\$ 1,626.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)).					+ 40.00
TOTAL FEES ENCLOSED					\$ 1,666.00

- a. A Check in the amount of \$1,666.00 to cover the above fees is enclosed.
- b. Please charge my Deposit Account No. 03-3975 in the amount of \$_____ to cover the above fees.
- c. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 03-3975.

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- 3. A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. is not required, as the application was filed in the United States Receiving Office (RO/US).
 - c. has been transmitted by the International Bureau.
- 4. A translation of the International Application into English (35 U.S.C. 371(c)(2)).
- 5. Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. have been transmitted by the International Bureau.
- 6. A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
- 7. An oath or declaration of the inventors (35 U.S.C. 371(c)(4)).
- 8. A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. § 371(c)(5)).
- 9. An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
- 10. An assignment document for recording.
PLEASE MAIL THE RECORDED ASSIGNMENT DOCUMENT TO:
 - a. the person whose signature, name and address appears at the bottom of the page.
 - b. the following:
- 11. The above checked items are being transmitted:
 - a. before the eighteenth (18th) month publication.
 - b. after publication of the Article 20 communication but before twenty (20) months from the priority date.
 - c. after twenty (20) months but before twenty-two (22) months (surcharge and/or processing fee included).
 - d. after twenty-two (22) months (surcharge and/or processing fee included).
 - e. by thirty (30) months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
 - f. after thirty (30) months but before thirty-two (32) months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date (surcharge and/or processing fee included).
 - g. after thirty-two (32) months (surcharge and/or processing fee included).
- 12. At the time of transmittal, the time limit for amending claims under Article 19:
 - a. has expired and no amendments were made.
 - b. has not yet expired.
- 13. Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely.
- 14. Applicants do not request expedited handling of this application and do not request that the National Stage of processing be commenced prior to the expiration of the applicable time limits under Article 22(1) or (2), or under Article 39(1)(a) of the PCT. 35 U.S.C. 371(f).

MICHAEL A. SANZO
 NAME
 PILLSBURY MADISON & SUTRO
 ADDRESS
 1100 NEW YORK AVE, N.W., NINTH FLOOR - EAST TOWER, WASHINGTON, DC 20005-3918

Michael A. Sanzo
 SIGNATURE
 36,912
 REGISTRATION NUMBER

RECORDED

NOVEL COMPOUNDSField of the invention

5 The present invention is related to novel compounds, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful in therapy, and in particular for the treatment of pain.

Background and prior art

10

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to possess immunomodulatory activities.

15

The identification of at least three different populations of opioid receptors (μ , δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

20

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. Some non-peptidic δ antagonists have been available for some time (see Takemori and Portoghese, 1992, Ann. Rev. Pharmacol. Tox., 32: 239-269. for review). These compounds, e.g. naltrindole, suffer from
25 rather poor (i.e., < 10-fold) selectivity for the δ receptor vs. μ receptor binding and exhibit no analgesic activity, a fact which underscores the need for the development of highly selective non-peptidic δ ligands.

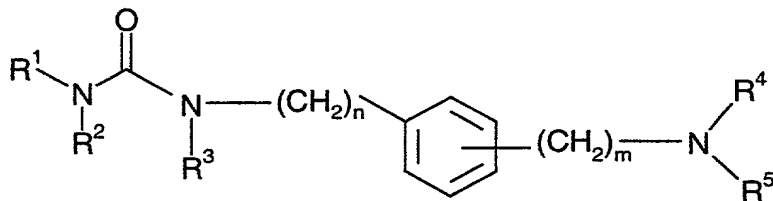
Thus, the problem underlying the present invention was to find new analgesics having improved analgesic effects, but also with an improved side-effect profile over current μ agonists and potential oral efficacy.

5 Analgesics that have been identified and are existing in the prior art have many disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that preferred compounds, described within the prior art, show significant convulsive effects when administered systemically.

10

The problem mentioned above has now been solved by developing novel 1,4-substituted phenyl compounds, as will be described below.

15 The novel compounds according to the present invention are defined by the general formula I



20 wherein

m and n is each and independently an integer of from 1-3, and one or more of the hydrogens in such an alkylene-chain may optionally be substituted by anyone of C₁ - C₆ alkyl, C₁ - C₆ alkoxy, or hydroxy; or

25 one or more of the methylene groups may optionally be substituted by a heteroatom such as O, N or S;

R^1 is selected from hydrogen, a branched or straight C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_8 cycloalkyl, C_4 - C_8 (alkyl-cycloalkyl) wherein the alkyl is C_1 - C_2 alkyl and the cycloalkyl is C_3 - C_6 cycloalkyl;

5

R^2 is selected from any of

(i) hydrogen;

10 (ii) a straight or branched C_1 - C_6 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl;

(iii) $-[(CH_2)_q-$ aryl];

(iv) $-[(CH_2)_r-$ heteroaryl] where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;

15 and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below; and wherein q and r is each and independently an integer of from 0 to 3;

(v) C_3 - C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally
20 substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;

and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

25 (vi) C_6 - C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

5

or

R¹ and R² may optionally form a heterocyclic ring;

R³ is selected from anyone of

10

(i) hydrogen;

(ii) a straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

15

(iii) -[(CH₂)_q-aryl] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

20

(iv) heteroaryl-(C₅ - C₁₀ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

5

(v) C₃-C₁₀ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined

10

(vi) -[(C₃-C₆ cycloalkyl)-(CH₂)_q] wherein q is an integer of from 1 to 3;

R⁴ is selected from

15

(i) hydrogen;

(ii) a straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

(iii) -[(CH₂)_q-aryl] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

25

(iv) heteroaryl-(C₅ - C₁₀ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

5

(v) C₃-C₁₀ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by

10

(vi) C₆-C₁₀ aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2

15

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted

20

R⁵ is selected from anyone of

(i) hydrogen;

25

(ii) a straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

(iii) -[(CH₂)_q-aryl] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the

30

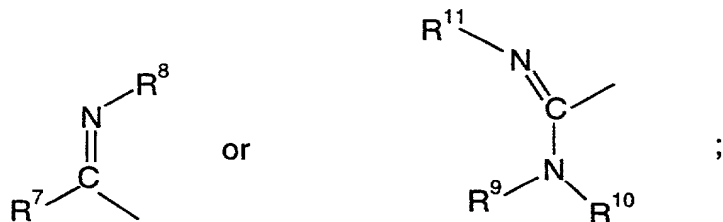
heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl

may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(iv) heteoaryl-(C₅ - C₁₀ alkyl), where the heteoaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteoaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(v) C₃-C₁₀ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteoaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteoaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi)



wherein

R⁷, R⁸, R⁹, R¹⁰ and R¹¹ is each and independently selected from

(a) hydrogen;

(b) a straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

(c) $-(\text{CH}_2)_q\text{-aryl}$] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(d) heteroaryl-($\text{C}_5 - \text{C}_{10}$ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(e) $\text{C}_3\text{-C}_{10}$ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(f) $\text{C}_6\text{-C}_{10}$ aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

or

R^4 and R^5 may optionally form a heterocyclic ring;

Y is each and independently selected from any of hydrogen, CH₃; —(CH₂)_{p1}CF₃;
 halogen; C₁-C₃ alkoxy; hydroxy; -NO₂; -OCF₃; —CONR^aR^b; —COOR^a;
 —COR^a; —(CH₂)_{p2}NR^aR^b; —(CH₂)_{p3}CH₃, (CH₂)_{p4}SOR^aR^b; —(CH₂)_{p5}SO₂R^a;
 —(CH₂)_{p6}SO₂NR^a; C₄-C₈(alkyl-cycloalkyl) wherein alkyl is C₁-C₂ alkyl and
 5 cycloalkyl is C₃-C₆ cycloalkyl; 1 or 2 heteroaryl(s) having from 5 to 10 atoms and
 the heteroatom(s) being selected from any of S, N and O; and oxides such as
 N-oxides or sulfoxides; and wherein

R^a and R^b is each and independently selected from hydrogen, a branched or straight
 10 C₁-C₆ alkyl, C₁-C₆ alkenyl, C₃-C₈ cycloalkyl; and wherein
 p¹, p², p³, p⁴, p⁵ and p⁶ is each and independently 0, 1 or 2.

Within the scope of the invention are also pharmaceutically acceptable salts of the
 compounds of the formula I, as well as isomers, hydrates, isoforms and prodrugs thereof.

15 Examples of heterocyclic ring systems which may be formed by R² and R³ together
 include but are not limited to azeridine, pyrrolidine, piperidine, azepine, azocine, their
 hydrogenated or dehydrogenated derivatives, their aminoderivatives and other aza-
 20 heterocycle moieties and their derivatives, such as dihydroimidazoles, di-, tetra- and
 hexahydropyrimidines and the like.

Preferred compounds according to the invention are compounds of the formula I
 wherein

25 m=n=1

R¹ is selected from

- (i) hydrogen;
- (ii) a branched or straight C₁-C₆ alkyl; or
- (iii) C₃-C₈ cycloalkyl;

5

R² is selected from any of

- (i) hydrogen;
- (ii) a straight or branched C₁-C₆ alkyl;

10 (iii) -[(CH₂)_q- aryl];

(iv) -[(CH₂)_r- heteroaryl] where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;

and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above; and wherein q and r is each and
15 independently an integer of from 0 to 3;

(v) C₃-C₆ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;

20 and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(vi) C₆-C₁₀ aryl, optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

25

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

5 or

R^1 and R^2 may optionally form a heterocyclic ring;

R^3 is selected from anyone of

10

(i) hydrogen;

(ii) a straight or branched C_1 - C_6 alkyl;

(iii) $-[(CH_2)_q\text{-aryl}]$ wherein q is an integer of from 0 to 3, and wherein the aryl may
15 optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

20 (iv) heteroaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

25 (v) C_3 - C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(vi) -[(C₃-C₆ cycloalkyl)-(CH₂)_q] wherein q is an integer of from 1 to 3;

R⁴ is selected from

5

(i) hydrogen;

(ii) a straight or branched C₁-C₆ alkyl;

(iii) -[(CH₂)_q-aryl] wherein q is an integer of from 0 to 3, and wherein the aryl may
10 optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(iv) heteroaryl-(C₅ - C₁₀ alkyl), where the heteroaryl has from 5 to 10 atoms and the
15 heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(v) C₆-C₁₀ aryl, optionally and independently substituted by one or more heteroaryl(s)
20 having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

25

R⁵ is selected from anyone of

(i) hydrogen;

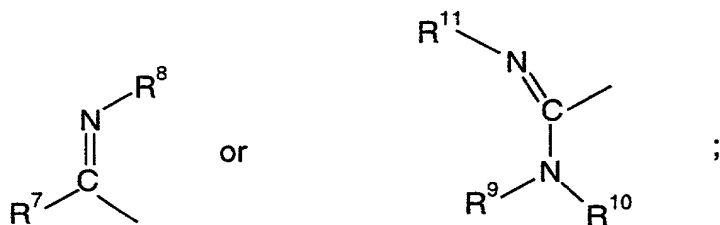
(ii) a straight or branched C₁-C₆ alkyl;

(iii) -[(CH₂)_q-aryl] wherein q is 0 or 1, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(iv) heteoaryl-(C₅ - C₁₀ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(v) C₃-C₆ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(vi)



wherein

R⁷, R⁸, R⁹, R¹⁰ and R¹¹ is each and independently selected from

(a) hydrogen;

(b) a straight or branched C₁-C₆ alkyl or C₂-C₆ alkenyl;

(c) -[(CH₂)_q-aryl] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(d) heteroaryl-(C₅ - C₁₀ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(e) C₃-C₁₀ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(f) C₆-C₁₀ aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

or

R⁴ and R⁵ may form a heterocyclic ring which may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above.

Particularly preferred compounds according to the invention are compounds of the formula

I wherein

5 m=n=1

R^1 is selected from

(i) a straight or branched C_1 - C_6 alkyl; *or*

(ii) C_3 - C_8 cycloalkyl;

10

R^2 is selected from

(i) methyl; *or*

(ii) phenyl optionally substituted by 1 or 2 substituents Y wherein each Y is as defined above;

15

R^3 is selected from

(i) $-CH_2$ -phenyl, optionally substituted by 1 or 2 substituents Y where Y is as defined above;

20

(ii) $-CH_2$ -cyclohexyl or $-CH_2$ -cyclopentyl;

R^4 is selected from

(i) hydrogen; *or*

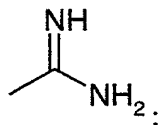
25 (ii) methyl;

R⁵ is selected from

(i) hydrogen;

(ii) methyl; *or*

5 (iii)



or

10 R⁴ and R⁵ together form a heterocyclic ring, optionally substituted by 1 or 2 substituents Y, where Y is as defined above.

By “halogen” we mean chloro, fluoro, bromo and iodo.

15

By “aryl” we mean an aromatic ring having 6 or 10 carbon atoms, such as phenyl and naphthyl.

By “heteroaryl” we mean an aromatic ring in which one or more of the from 5-10 atoms in
20 the ring are elements other than carbon, such as N, S and O.

By “isomers” we mean compounds of the formula (I), which differ by the position of their functional group and/or orientation. By “orientation” we mean stereoisomers, diastereoisomers, regioisomers and enantiomers.

25

By “isoforms” we mean compounds of the formula I which differ in the relative physical arrangement of molecules by crystal lattice, such that isoforms refer to various crystalline compounds and amorphous compounds.

By “prodrug” we mean pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is an active form of the drug. The reference by Goodman and Gilman, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, “Biotransformation of Drugs, p. 13-15, describing prodrugs generally, is hereby incorporated by reference.

The novel compounds of the present invention are useful in therapy, especially for the treatment of various pain conditions such as chronic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, urinary incontinence, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (eg. Amnesia, analgesia, muscle relaxation and sedation). Included in this

combination are inhaled anaesthetics, hypnotica, anxiolytics, neuromuscular blockers and opioids.

The compounds of the present invention in isotopically labelled form are useful as a
5 diagnostic agent.

Also within the scope of the invention is the use of any of the compounds according to the formula (I) above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

10

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula (I) above, is administered to a patient in need of such treatment.

15

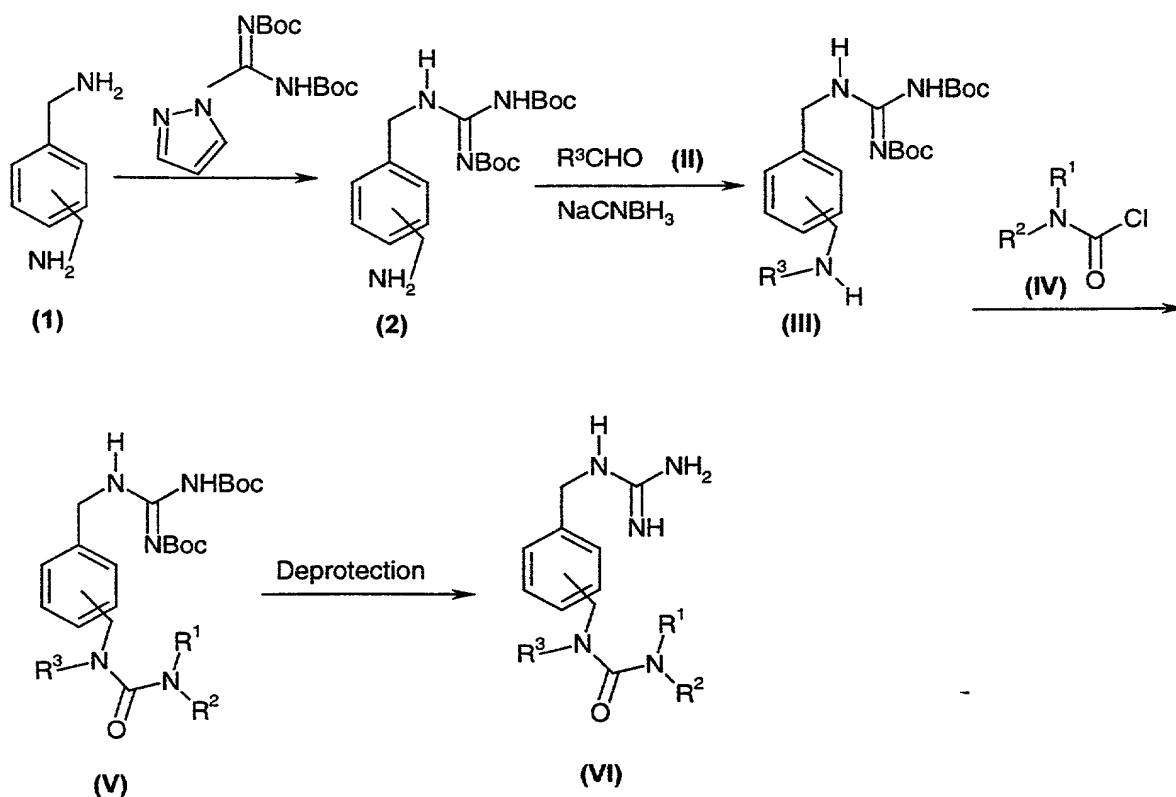
The best mode of performing the invention known at present, is to use the compounds according to Example 1 (compound 12) and Example 2 (compound 13). The numbering of the compounds is in accordance with the numbering in the Schemes presented in the following.

Methods of preparation

The compounds of the present invention may be prepared as described in Scheme 1 below.

5 General procedure for the preparation of 1,4 or 1,3-guanidinomethyl aminomethyl xylene

Scheme 1



10

As shown in Scheme 1 above, compounds of the formula VI may be obtained from commercially available bis-amino xylene (compound 1).

Compound 1 is converted into mono-(diBoc)-guanidinomethyl derivative 2 using a protected guanylation reagent such as 1-H-pyrazole-1-(N,N-bis (tert-butoxycarbonyl) carboxamidine in an organic solvent such as THF.

5 The secondary amine of the formula III may be generated using a reductive amination step, where compound 2 is reacted with an aldehyde II in the presence of an acid such as acetic acid or a Lewis acid such as ZnCl₂, in a protic solvent such as methanol or ethanol in the presence of a reducing agent such as sodium cyanoborohydride.

10 Compounds of the formula V may be obtained by performing an urea formation using compound III with a chloroformate of the formula IV in a solvent such as methylene chloride and in the presence of a tertiary amine as base, such as triethylamine.

15 Finally, a compound of the formula VI may be obtained by cleavage of the Boc protecting group with an acid such as aqueous hydrochloric acid or by using organic acid such as trifluoroacetic acid in a solvent such a methylene chloride.

The invention will now be described in more detail by way of the following Examples, which are not to be construed as limiting the invention in any way.

20

Step 1 (a)

Preparation of 1-(diBoc)-guanidinomethyl-4-aminomethyl benzene (compound 2)

Part A

25 1-H-pyrazole-1-carboxamidine was prepared according to Bernatowicz et.al., J. Org. Chem. 1992, 57, pp.2497-2502, and protected with di-*tert*-butyl dicarbonate to give 1-H-pyrazole-1-N,N-bis(tert-butoxycarbonyl)carboxamidine (compound 1) according to *Drake et.al, Synth. 1994. pp.579-582.*

30

Part B

To a solution of *p*-xylylenediamine (compound 1) (30.8 g, 0.226 mol) in THF (300 mL) was added a solution of 1-H-Pyrazole-1-(*N,N*-bis(tert-butoxycarbonyl)carboxamidine (35.0 g, 0.113 mol) in THF (100 mL). The solution was stirred at room temperature for 3 h.

5 The solvent was removed under reduced pressure. Water was added to the residue and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated. The product (compound 2) was purified by column chromatography on silica gel using a mixture of methylene chloride:methanol as the eluent to give 24.3 g (57 % yield) of 1-(diBoc)-guanidinomethyl-4-aminomethyl

10 benzene (compound 2 where NH₂ is in 4-position).

¹H NMR (CDCl₃) δ 8.5 (broad s, 1H), 7.32 (s, 4H), 4.65 (d, 2H), 3.89 (s, 2H), 1.5 (s, 9H), 1.48 (s, 9H).

15

Step 1 (b)**Preparation of 1-(diBoc)-guanidinomethyl-3-aminomethyl benzene**

1-(diBoc)-guanidinomethyl-3-aminomethyl benzene was prepared in a similar fashion from *m*-xylylenediamine and of 1-H-Pyrazole-1-(*N,N*-bis(tert-butoxycarbonyl)carboxamidine.

20

¹H NMR (CDCl₃) δ 8.52 (broad s, 1H), 7.28-7.08 (m, 4H), 4.56 (d, 2H), 3.81 (s, 2H), 1.42 (s, 9H), 1.39 (s, 9H).

Step 2**Reductive amination: Preparation of 1-(diBoc)-guanidinomethyl-4-[N-(cyclohexylmethyl)]benzene (compound 2 where NH₂ is in 3-position)**

5 To a methanolic solution (15 ml) of compound 2 where the amino group is in 4-position (341 mg, 0.90 mmol) and cyclohexanecarboxaldehyde (111.17 mg, 0.99 mmol) was added zinc chloride (122.79 mg, 0.90 mmol) and sodium cyanoborohydride (67.93 mg, 1.08 mmol). The mixture was stirred over night under nitrogen, whereafter the mixture was diluted with saturated aqueous sodium bicarbonate, and extracted with methylene chloride.

10 The organic phase was washed with brine, dried over MgSO₄ and concentrated. This crude product was further purified by silica gel chromatography using CH₂Cl₂/MeOH (95:5) as the solvent, to give 164 mg of the pure desired product (compound 2 where NH₂ is in 3-position).

15 ¹H NMR (CDCl₃)

δ (ppm): 0.83 (2H, m, cyclohexane ring); 1.10 (3 H, m, cyclohexane ring); 1.42 (9H, s, boc), 1.46 (9H, s, boc), 1.65 (6H, m, cyclohexane ring), 2.41 (2H, d, *J*=6.8 Hz, C₆H₁₁ - CH₂), 3.72 (2H, s, C₆ H₄ - CH₂), 4.54 (2H, d, *J*=5.6 Hz, NNCNH - CH₂ - C₆H₄), 7.18~7.25 (4H, m, Ar), 8.50 (1H, br, NH - CNN) ppm.

20

Specific examples illustrating the preparation of secondary amines, i.e. intermediates of the formula III, are provided in Table 1 below.

Table 1

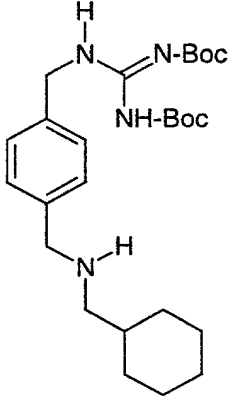
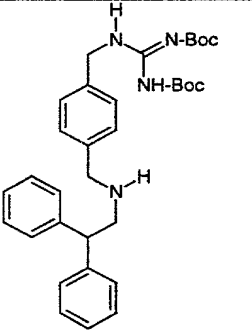
Inter- mediate no.	Intermediate of the formula III and chemical name	Aldehyde [R ³ CHO]	Characterization data
3		cyclohexane carboxaldehyde	¹ H NMR (CDCl ₃) δ. (ppm): 0.83 (2H, m, cyclohexane ring); 1.42 (9H, s, boc), 1.46 (9H, s, boc), 1.65 (6H, m, cyclohexane ring), 2.41 (2H, d, J=6.8 Hz, C ₆ H ₁₁ - CH ₂), 3.72 (2H, s, C ₆ H ₄ - CH ₂), 4.54 (2H, d, J=5.6 Hz, NNCNH - CH ₂ - C ₆ H ₄), 7.18 - 7.25 (4H, m, Ar), 8.50 (1H, br, NH - CNN) ppm.
4	 <p data-bbox="402 1661 670 1848">1-(diBoc)-guanidino methyl-4-[N-(2,2- diphenylethyl)aminom ethyl] benzene</p>	Diphenyl- benzaldehyde	¹ H NMR (CDCl ₃) δ 8.5 (broad s, 1H), - 7.23-7.14 (m, 14H), 4.58 (d, 2H), 4.18 (t, 1H), 3.78 (s, 2H), 3.22 (d, 2H), 1.50 (s, 9H), 1.47 (s, 9H). MS(FAB⁺): 559 (M+H), 359.

Table 1 (Contd.)

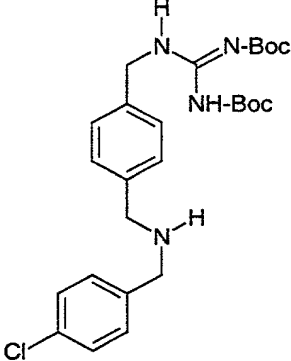
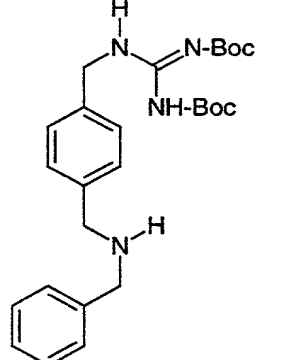
Inter- mediate no.	Intermediate of the formula III and chemical name	Aldehyde [R ³ CHO]	Characterization data
5	 <p>1-(diBoc)-guanidino- methyl-4-[N-(4- chlorobenzyl) aminomethyl] benzene</p>	4-chloro- benzaldehyde	¹H NMR (DMSO-d₆) δ 8.6 (broad t, 1H), 7.42-7.1 (m, 10H), 4.52 (t, 2H), 3.7 (s, 2H), 3.2 (s, 2H), 1.5 (s, 9H), 1.45 (s, 9H). MS(FAB⁺): 503 (M+H), 403, 303.
6	 <p>1-(diBoc)-guanidino- methyl-4-[N-(benzyl) aminomethyl] benzene</p>	Benzaldehyde	¹H NMR (CDCl₃) δ 7.2 (m, 9H), 4.5 (s, 2H), 4.15 (t, 2H), 3.7 (s, 2H), 1.5 (s, 18H).

Table 1 (Contd.)

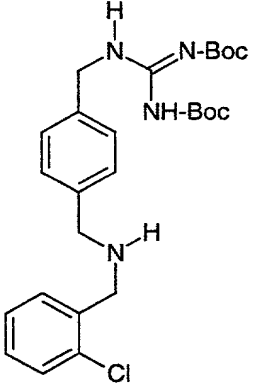
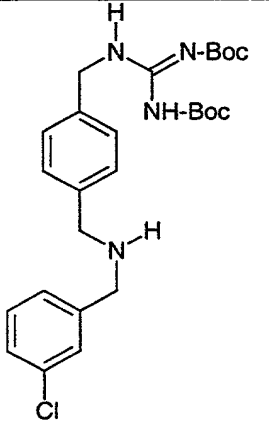
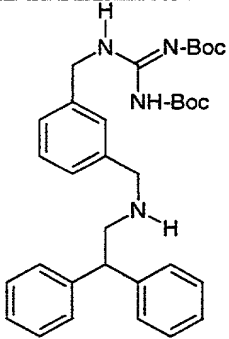
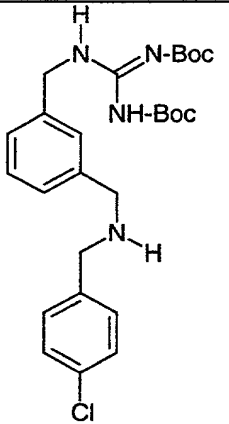
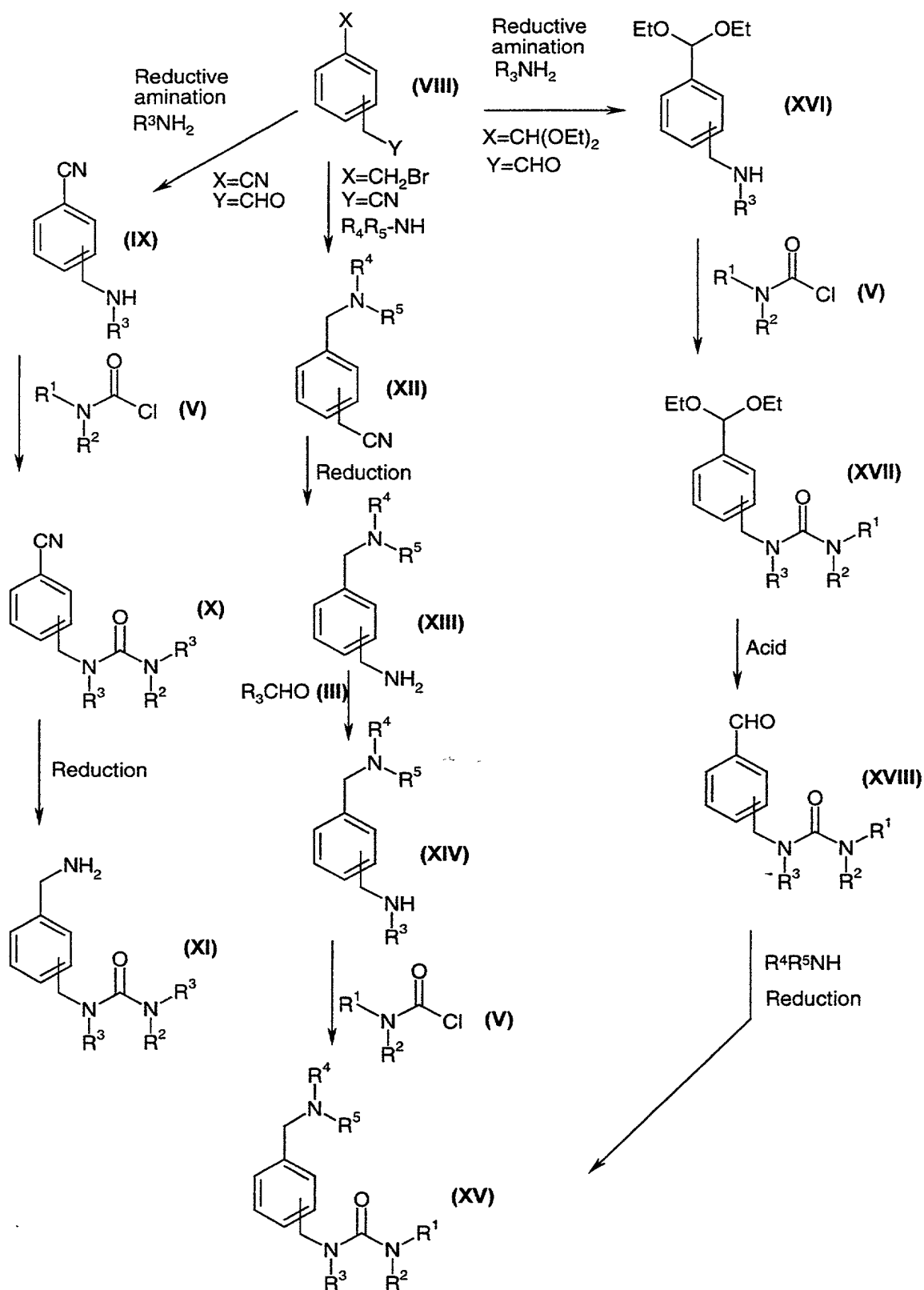
Inter- mediate no.	Intermediate of the formula III and chemical name	Aldehyde [R ³ CHO]	Characterization data
7	 <p>1-(diBoc)-guanidino- methyl-4-[N-(2- chloro- benzyl)aminomethyl] benzene</p>	2-chloro- benzaldehyde	¹H NMR (CDCl₃) δ 8.62 (broad s, 1H), 7.48-7.1 (m, 8H), 4.62 (d, 2H), 3.95 (s, 2H), 3.85 (s, 2H), 1.53 (s, 9H), 1.5 (s, 9H).
8	 <p>1-(diBoc)-guanidino- methyl-4-[N-(3- chloro- benzyl)aminomethyl] benzene</p>	3-chlorobenz- aldehyde	¹H NMR (CDCl₃) δ 8.56 (broad t, 1H), 7.4-7.15 (m, 8H), 4.6 (d, 2H), 3.8 (s, 4H), 1.56 (s, 9H), 1.52 (s, 9H). MS(APCI): 503 (M+H), 403, 303.

Table 1 (Contd.)

Inter- mediate no.	Intermediate of the formula III and chemical name	Aldehyde [R ³ CHO]	Characterization data
9	 <p>1-(diBoc)-guanidino- methyl-3-[N-(2,2- diphenylethyl) aminomethyl] benzene</p>	Diphenylacet- aldehyde	MS(ES ⁺): 559 (M+H), 459, 359.
10	 <p>1-(diBoc)-guanidino- methyl-3-[N-(4- chloro-benzyl) aminomethyl] benzene</p>	4-chlorobenz- aldehyde	¹H NMR (CDCl₃) δ 8.48 (broad s, 1H), 7.3-6.96 (m, 8H), 4.68-4.32 (m, 4H), 3.78-3.6 (m, 2H).

Scheme 2



Alternatively, as shown in Scheme 2, compounds of the formula (XI) may be obtained by using compounds of the formula (VIII) wherein $X=CN$ and $Y=CHO$, as a starting material.

A reductive amination using a primary amine with compound (VIII) in the presence of an acid such as acetic acid, and in the presence of a reducing agent such as sodium cyanoborohydride in a solvent such as methanol or ethanol, provides a compound of the formula (IX).

Compounds of the formula (X) may be obtained by performing an urea reaction using compounds of the formula (IX) with a chloroformate of the formula (V) in a solvent such as methylene chloride and in the presence of a tertiary amine as base, such as triethylamine.

Compounds of the formula (XI) may be prepared by a reduction of the nitrile function in formula (X), using a reduction agent such as borane-THF complex in a solvent such as THF.

Compounds of the formula (XV) may be prepared by reacting compounds of the formula (VIII) wherein $X=CH_2Br$ and $Y=CN$, with an amine in a solvent such as acetonitrile, providing a compound of the formula (XII). A reduction of the nitrile function using a reducing agent such as borane-THF complex in a solvent such as THF, provides the primary amine of the formula (XIII).

A reductive amination step of (XIII) as described above, provides a compound of the formula (XIV). Finally, urea formation of the secondary amine (XIV) as described above, provides a compound of the formula (XV).

Alternatively, compounds of the formula (XV) may be prepared by using a monoprotected dialdehyde such as a compound of the formula (VIII) wherein $X=CH(OEt)_2$ and $Y=CHO$, and a reductive amination in the presence of a reducing agent such as sodium cyanoborohydride in a solvent such as methanol or ethanol. Urea formation as described

above provides a compound of the formula (XVII). Hydrolysis of the diethyl acetal function in compound (XVII) using an acid such as TFA in a solvent such as methylene chloride, provides the corresponding aldehyde (XVIII).

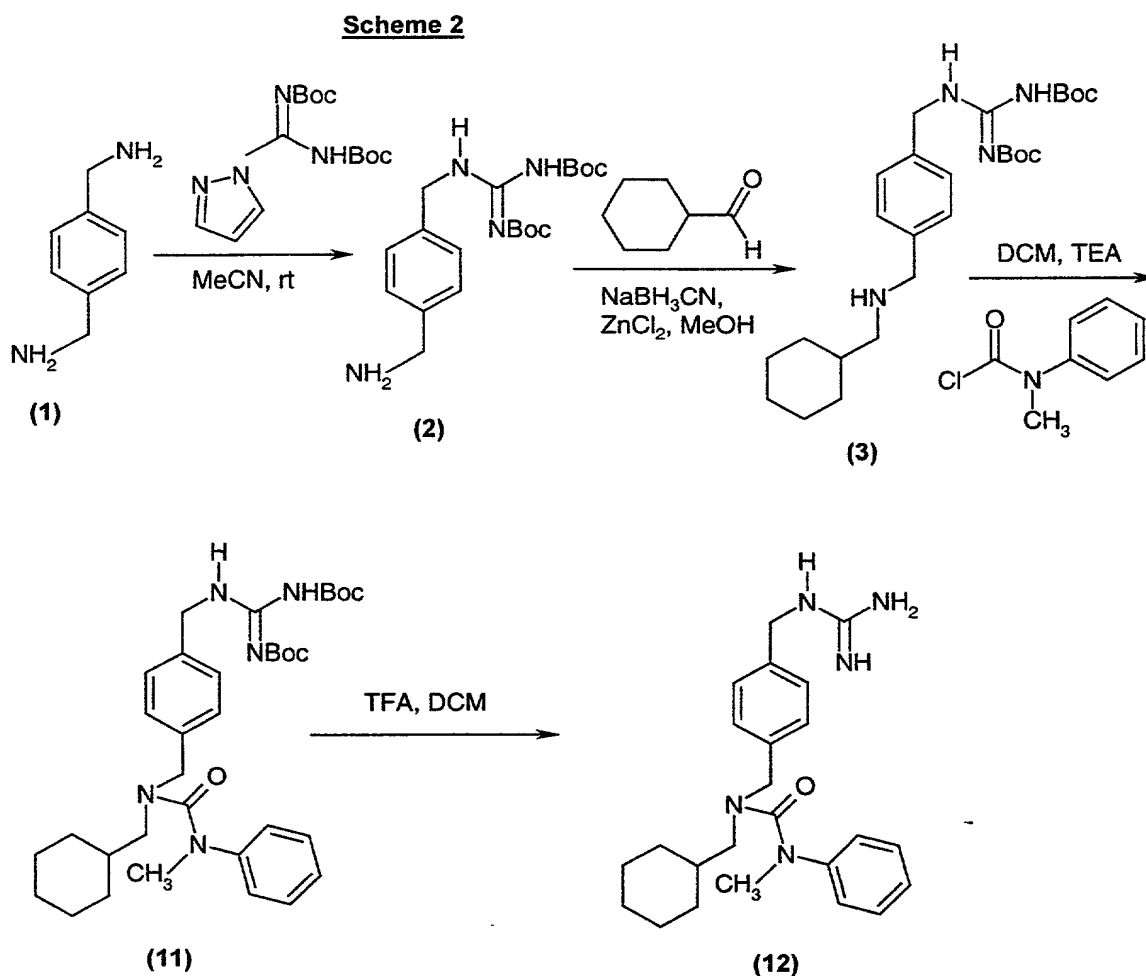
- 5 Finally, a reductive amination as described before, provides compounds of the formula (XV).

The invention will now be described in more detail by the following Examples, which are
 10 not to be construed as limiting the invention.

COPTOSUS

EXAMPLE 1**Preparation of 1-N-(cyclohexylmethyl)-N-(N-methyl-N-phenylcarbamoyl)-aminomethyl-4-guanidinomethyl-benzene (Compound 12)**

Compound 12 of the present Example was prepared by following the synthetic route described in Scheme 2 below.



- 10 To a solution of compound 3 (164 mg, 0.35 mmol) in methylene chloride (10 ml) was added N-methyl-N-phenyl carbamoylchloride (120.78 mg, 0.71 mmol) and triethylamine (71.90 mg, 0.71 mmol). The mixture was stirred at room temperature for 3 h, washed with a saturated NH_4Cl aqueous solution and brine, dried over MgSO_4 and concentrated to give

the crude product (compound 11). This crude compound was used directly without purification for the preparation of compound 12. It was dissolved in dry methylene chloride (3 ml), 1.5 ml of TFA was added and the reaction mixture was stirred at room temperature for 1 hour. The excess of solvent and TFA was evaporated, the residue was purified by
5 reverse phase preparative HPLC to give the pure desired product (100 mg, 71 % in 2 steps).

¹H NMR (CDCl₃) δ (ppm): 0.70 (2H, m, cyclohexane ring); 1.10 (3H, m, cyclohexane ring); 1.41 (3H, m, cyclohexane ring); 1.53 (3H, m, cyclohexane ring); 2.72 (2H, d, *J*=6.4 Hz, C₆H₇ - CH₂), 3.00 (3H, s, N-CH₃), 4.13 (2H, s, C₆H₄ - CH₂), 4.24 (2H, d, *J*=4.8 Hz, NH-CH₂-Ph), 6.93–7.25 (9H, m, Ar), 8.13 (1H, br, NH-C=N).

MS Observed (CI): 408.45 (MH⁺).

15 The following specific compounds were prepared by following the synthesis description described above.

20 **EXAMPLES 2-7**

The following compounds were prepared by using the same procedure as described in Example 1, but using the intermediate and acid chloride indicated in Table 2 below.

Table 2

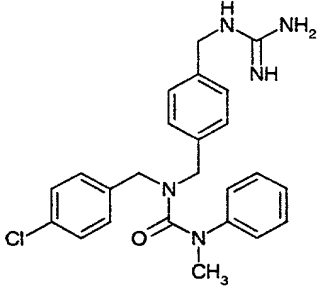
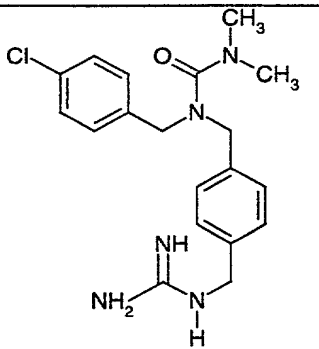
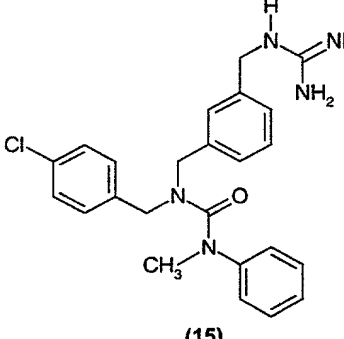
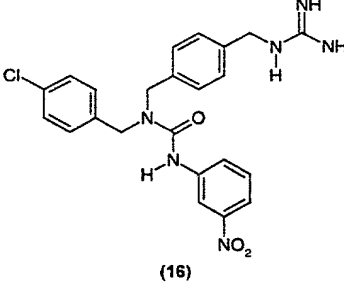
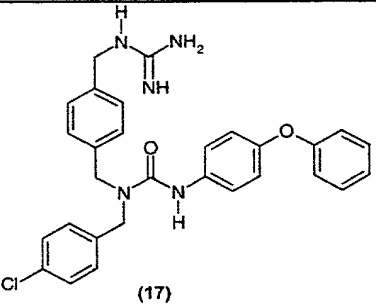
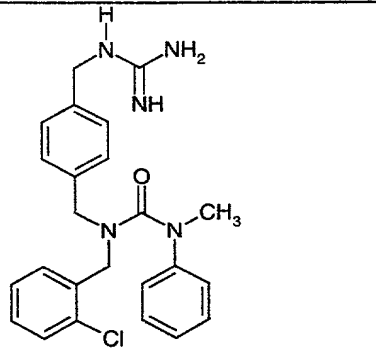
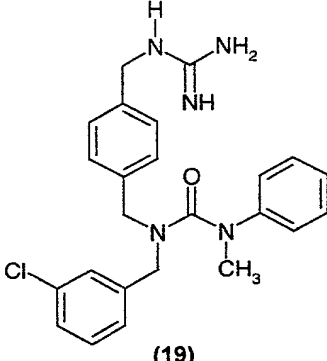
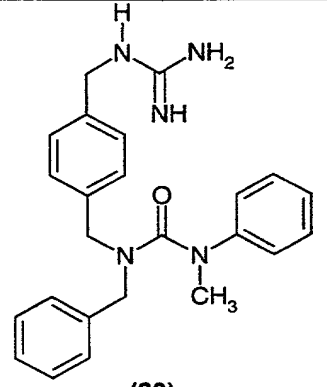
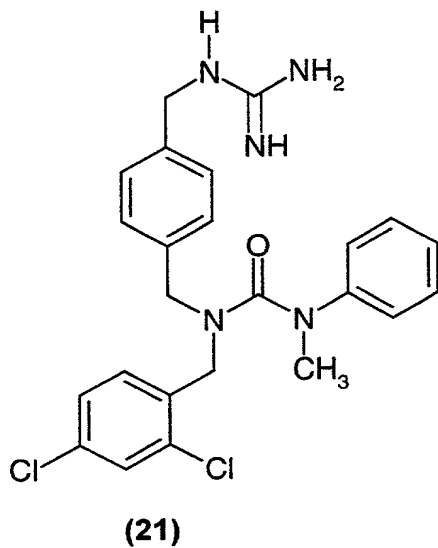
Ex.	Structure and chemical name	Inter Mediate	Carbamoyl Chloride or Isocyanate	Physical Characterization
2	 <p>(13)</p> <p>1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenyl-carbamoyl)]-aminomethyl-4-guanidino-benzene</p>	5	N-methyl-N-phenyl carbamoyl chloride	$^1\text{H NMR (DMSO-d}_6\text{)}$ δ 8.0 (t, 1H), 8.6-8.2 (m, 14H), 4.4 (d, 2H), 4.2 (d, 4H), 3.1 (s, 3H).
3	 <p>(14)</p> <p>1-N-[(4-chlorobenzyl)-N-(N,N-dimethyl carbamoyl)]-aminomethyl-4-guanidinomethyl-benzene</p>	5	Dimethylcarbamoylchloride	$^1\text{H NMR (DMSO-d}_6\text{)}$ δ 8.1 (broad, 1H), 7.4 (d, 2H), 7.25 (d, 2H), 7.15 (m, 4H), 4.35 (d, 2H), 4.15 (d, 4H), 2.85 (s, 6H). MS(APCI): 374 (M+H).

Table 2contd.

Ex.	Structure and chemical name	Inter Mediate	Carbamoyl Chloride or Isocyanate	Physical Characterization
4	 <p>(15)</p> <p>1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenyl-carbamoyl)]-aminomethyl-3-guanidinomethyl-benzene</p>	10	N-methyl-N-phenyl carbamoyl chloride	¹ H NMR (CDCl ₃) δ 7.05-7.5 (m, 13H), 4.4 (broad s, 2H), 4.15 (s, 2H), 3.35 (s, 3H), 3.05 (d, 2H). MS(APCI): 436 (M+H)
5	 <p>(16)</p> <p>1-N-[(4-chlorobenzyl)-N-(3-nitrophenyl-carbamoyl)]-aminomethyl-4-guanidinomethyl-benzene</p>	5	3-nitrophenyl-isocyanate	¹ H NMR (DMSO-d ₆) δ 9.2 (s, 1H), 8.6 (s, 1H), 8.1 (broad, 1H), 8.0 (d, 1H), 7.7 (d, 1H), 7.55 (t, 1H), 7.4 (d, 1H), 7.2 (m, 6H), 4.7 (d, 4H), 4.3 (d, 2H). MS(APCI): 466 (M+H)

Ex.	Structure and chemical name	Inter- medi- ate	Carbamoyl Chloride or Isocyanate	Physical Characterization
6	 <p>(17)</p> <p>1-N-[(4-chlorobenzyl)-N-(4-phenoxy-carbamoyl)]-aminomethyl-4-guanidino-methyl-benzene</p>	5	4-phenoxy-phenyl-isocyanate	¹ H NMR (DMSO-d ₆) δ 8.8 (s, 1H), 7.8-7.5 (m, 12H), 7.1 (t, 1H), 6.9 (d, 4H), 4.5 (d, 4H), 4.3 (d, 2H). MS(APCI): 514. (M+H)
7	 <p>(18)</p> <p>1-N-[(2-chlorobenzyl)-N-(N-methyl-N-phenyl-carbamoyl)]-aminomethyl-4-guanidinomethyl-benzene</p>	7	N-methyl-N-Phenylcarbamoyl-chloride	¹ H NMR (DMSO-d ₆) δ 8.2 (broad, 1H), 7.4-6.95 (m, 13H), 4.5 (s, 2H), 4.2 (d, 4H), 3.1 (s, 3H). MS(APCI): 436. (M+H).

Ex.	Structure and chemical name	Inter- medi- ate	Carbamoyl Chloride or Isocyanate	Physical Characterization
8	 <p>(19)</p> <p>1-N-[(3-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-guanidinomethyl-benzene</p>	8	N-methyl-N-phenylcarbamoyl chloride	<p>¹H NMR (DMSO-d₆) δ 8.2 (broad, 1H), 7.4-7.1 (m, 13H), 4.35 (d, 2H), 4.15 (s, 4H), 3.1 (s, 3H).</p> <p>MS(APCI): 436. (M+H).</p>
9	 <p>(20)</p> <p>1-N-[(benzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-guanidinomethyl-benzene</p>	6	N-methyl-N-phenylcarbamoyl chloride	<p>¹H NMR (DMSO-d₆) δ 8.1(t, 1H), 7.3 (m, 8H), 7.05 (m, 6H), 4.45 (d, 2H), 4.05 (d, 4H), 3.15 (s, 3H).</p>

EXAMPLE 10**Preparation of 1-N-[(2,4-dichlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-guanidinomethyl-benzene (Compound 21)**

Following the same procedure as described in Example 1, step 2 but substituting 2,4-dichlorobenzaldehyde for cyclohexanecarboxaldehyde, the title compound 21 was
10 obtained.

$^1\text{H NMR (DMSO-}d_6)$ δ 8.2 (broad, 1H), 7.5-7.1 (m, 12H), 4.5 (d, 2H), 4.2 (s, 4H), 3.1 (s, 3H).

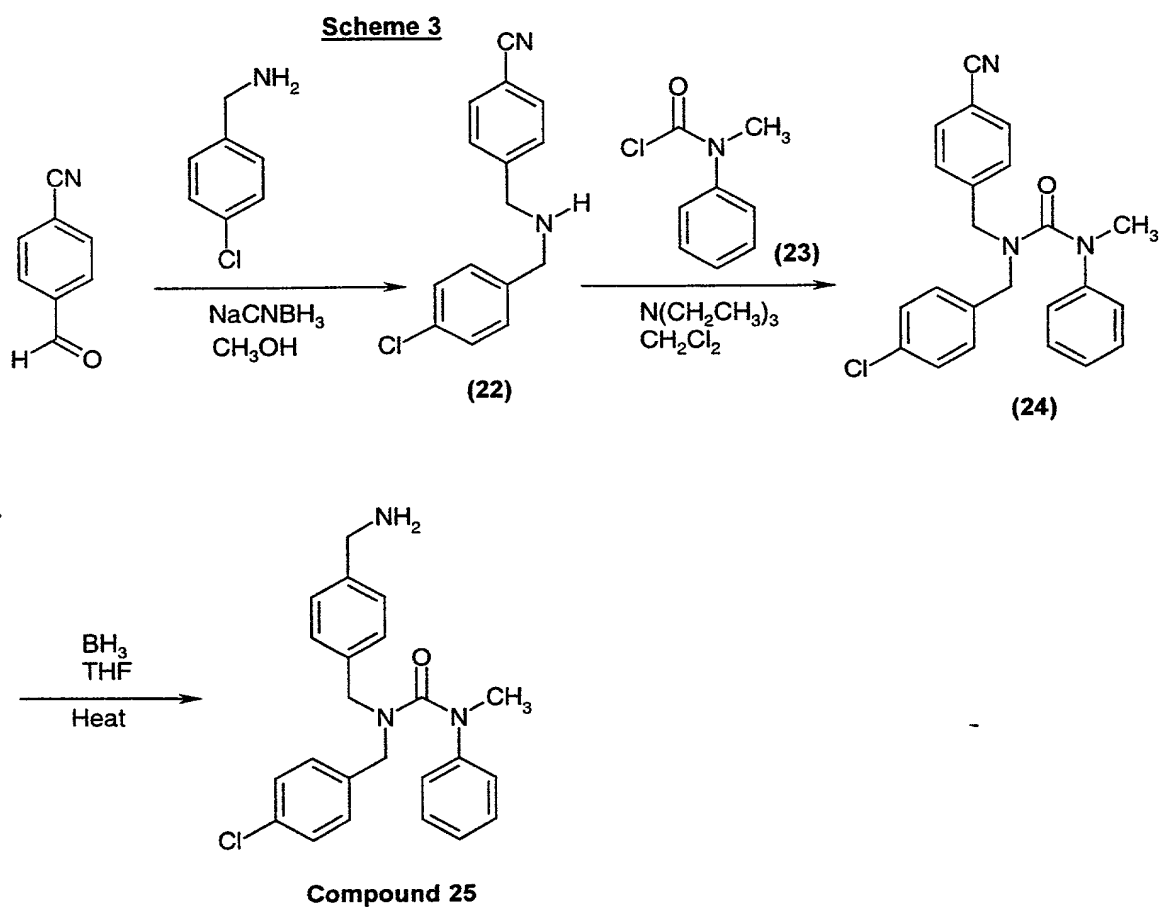
MS(APCI): 469.95 (M+H).

15

EXAMPLE 11**Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-aminomethyl-benzene (Compound 25)**

5

Compound 25 of the present Example was prepared by following the procedure described in Scheme 3 below.



10

Step 1**Preparation of N-(4-chlorobenzyl)-4-cyanobenzyl amine (compound 22)**

To a methanolic solution (20 mL) of 4-chlorobenzylamine (1.02 g, 7.2 mmol) was added successively ZnCl₂ (.981 g, 7.2 mmol), 4-cyanobenzaldehyde (1.007 g, 7.3 mmol), and NaCNBH₃ (0.452 g, 7.2 mmol). The reaction mixture was stirred at r.t. for 2 days. It was diluted with aq. sodium bicarbonate and the reaction mixture was extracted with methylene chloride. The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated. The product (compound 22) was purified by silica gel chromatography: 1.43 g (77%).

¹H NMR (CDCl₃) δ 7.45 (d, 2H), 7.28 (d, 2H), 7.10 (s, 4H), 3.68 (s, 2H), 3.58 (s, 2H).

Step 2**Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-cyanobenzene (compound 24)**

To a solution of N-(4-chlorobenzyl)-4-cyanobenzyl amine (compound 22)(1.43 g, 5.57 mmol) in dioxane (20 mL) was added N-methyl-N-phenyl carbamoyl chloride (compound 23) (1.039 g, 6.12 mmol) and triethylamine (0.853 mL, 6.12 mmol). The reaction mixture was stirred at r.t. for 1 day, then it was diluted with ethyl acetate and washed with 10% HCl, saturated sodium bicarbonate, water, brine, dried over MgSO₄ and concentrated to give compound 24: 1.95 g (89%).

Step 3**Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-aminomethyl-benzene (compound 25)**

To a THF (6 mL) solution of 1-N-[(4-chlorobenzyl)-N',N'-(methyl, phenyl)carbamoyl]-aminomethyl-4-cyanobenzene (compound 24) (0.39 g, 1 mmol) was added a 1M BH₃.THF complex (2.2 mL). The mixture was heated at 90 °C overnight. Then a 2.55 M HCl in methanol (3 mL) was added and the reaction mixture was heated at reflux for 1 h. The

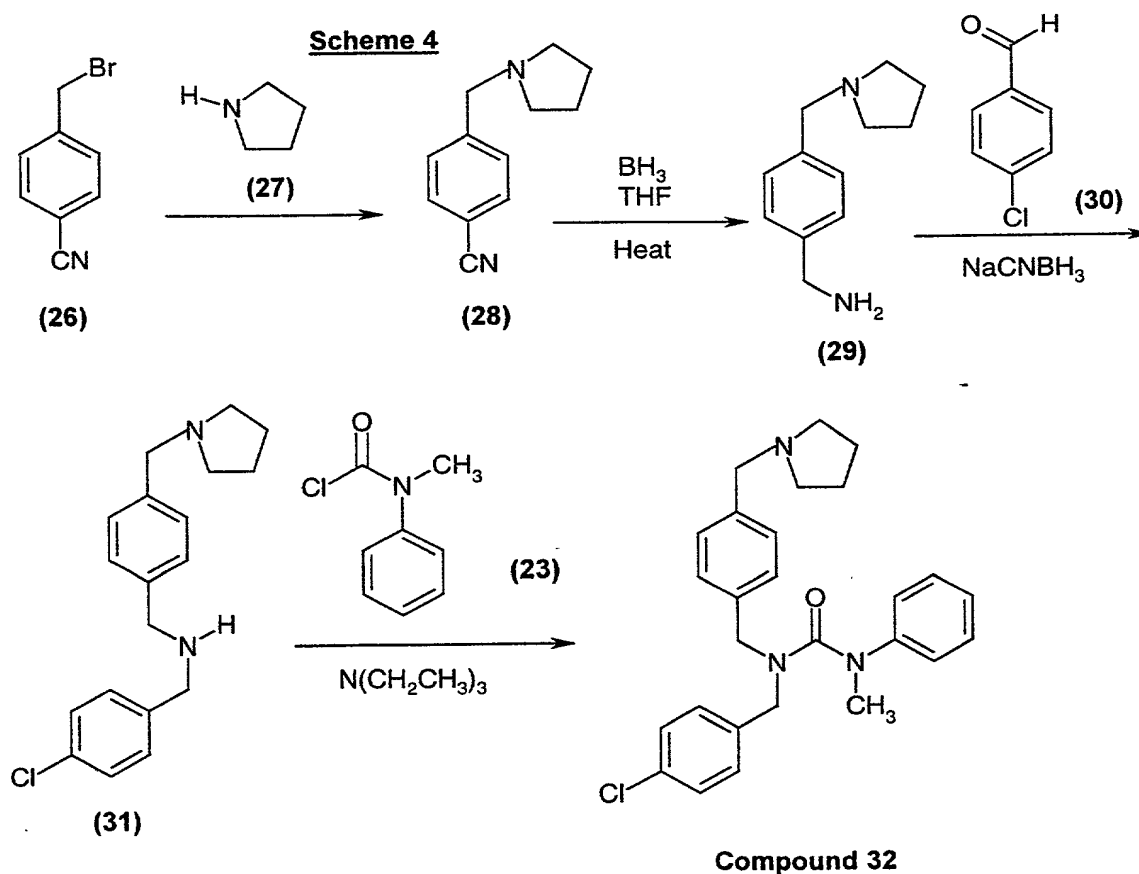
mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over MgSO_4 and concentrated. The product (compound 25) was purified by preparative TLC using methanol/methylene chloride/ammonium hydroxide as the eluent.

- 5 $^1\text{H NMR}$ (CDCl_3) δ 7.20-6.84 (m, 13H), 4.00 (s, 4H), 3.70 (s, 2H), 3.05 (s, 3H), 2.05 (broad s, 2H). MS: 394. (M+H).

EXAMPLE 12

- 10 Preparation of 1-N-[4-chlorobenzyl]-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-(N-pyrrolidinomethyl)-benzene (compound 32)

The compound 32 of Example 11 was prepared by following the procedure described in Scheme 4 below.



Step 1**Preparation of 4-cyano-1-N-pyrrolinomethyl benzene (compound 28)**

4-cyano benzyl bromide (compound 26) (20.0 g, 0.102 mol) was dissolved in
5 acetonitrile(100 mL) and added to a cooled (0° C) solution of pyrrolidine (compound 27)
(8.5 g, 0.12 mol) in acetonitrile. The mixture was stirred at RT for 3 days. The reaction
mixture was acidified with 4N HCl and washed with ethyl acetate. The aqueous layer was
basified with 20% sodium hydroxide and extracted with ethyl acetate. The organic layer
was concentrated to give product (compound 28)(11.0 g, 58%) which was carried on to
10 the next step with no further purification.

¹H-NMR (CDCl₃) δ; 7.6 (d, 2H), 8.4 (d, 2H), 3.55 (s, 2H), 2.55 (t, 2H), 1.7 (t, 2H). MS:
187. (M+H)

Step 2

15 **Preparation of 4-N-aminomethyl-1-N-pyrrolinomethyl benzene (compound 29)**
4-cyanomethyl-1-N-pyrrolinomethyl benzene (compound 28) (11 g, 59 mmol) was
dissolved in dry THF(20 mL). To this solution was added a 1M solution of borane/THF
complex (180 mL). The mixture was refluxed overnight. The solution was then cooled to
r.t. and a solution of 3N HCl in methanol (120 mL) was added dropwise. The mixture was
20 again refluxed overnight. After cooling to room temperature, the product (compound 29)
fell out of solution as white precipitate and was collected and washed with THF: 11.6 g.

¹H NMR (CDCl₃) δ 8.8 (broad, 1H), 7.6 (d, 2H), 7.4 (d, 2H), 4.4 (s, 2H), 4.0 (s, 2H), 3.3
(t, 2H), 3.0 (t, 2H), 2.0 (t, 4H).

25 **MS:** 191. (M+H)

Step 3**Preparation of N-(4-chlorobenzyl)-1-(1-N-pyrrolidinomethyl)-benzylamine
(compound 31)**

- 5 Following the same procedure as described for Example 10, step 1, but substituting
4-chlorobenzylamine for compound 29 and 4-cyanobenzaldehyde for
4-chlorobenzaldehyde, the title compound was obtained.

MS: 357 (M+H)

10

Step 4**Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-
aminomethyl-4-(1-N-pyrrolidinomethyl)-benzene (compound 32)**

15

- Following the procedure described in Example 10, step 2, but substituting compound 22
for compound 31, the title compound was obtained.

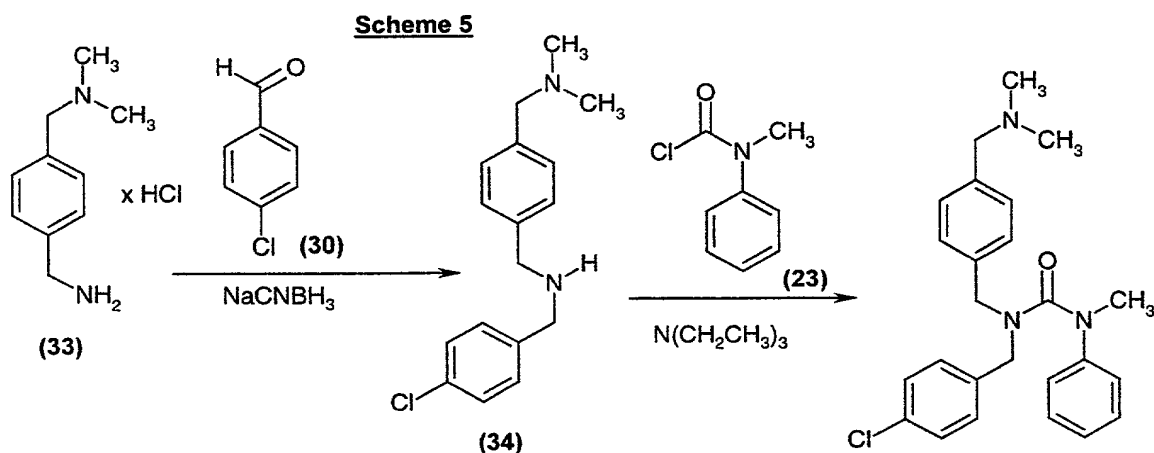
- 20 ¹H NMR (CDCl₃) δ 7.55 (d, 2H), 7.45 (d, 2H), 7.4 (d, 2H), 7.2 (d, 2H), 7.0 (d, 2H), 6.95
(d, 2H), 4.3 (d, 4H), 4.1 (s, 2H), 3.25 (s, 3H), 3.1 (t, 4H), 2.05 (t, 4H).

MS 448. (M+H)

25

EXAMPLE 13**Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-
aminomethyl-4-(N,N-dimethyl)-aminomethyl-benzene (compound 35)**

- The compound 35 of Example 12 was prepared by following the procedure described in
30 Scheme 5 below.

**Step 1****Preparation of 1-N-(4-chlorobenzyl)-4-(N,N-dimethyl)aminomethyl benzyl amine (compound 34)**

5 A round bottom flask was charged with 1-N-aminomethyl-4-N,N-dimethylaminomethyl benzene hydrochloride (compound 33) (2.36 g, 10 mmol), 4-chlorobenzaldehyde (compound 30) (1.51 g, 11 mmol, 97% pure), and methanol (40 mL). The mixture was stirred at r.t. for 20 minutes, then solid NaCNBH₃ was added and the reaction mixture was stirred at r.t. overnight. It was diluted with aqueous sodium bicarbonate, and extracted

10 with ethyl acetate. The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give 1.29 g of (compound 34) as an oily residue.

Step 2**Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-(N,N-dimethyl)-aminomethyl-benzene (compound 35)**

15 To a solution of 1-N-(4-chlorobenzyl)-4-(N,N-dimethyl)aminomethyl benzyl amine (compound 34) (0.562 g, 1.95 mmol) in dioxane (8 mL) was added triethylamine (0.326 mL, 2.34 mmol) and N-methyl,N-phenyl carbamoyl chloride (compound 23) (0.395 g, 2.34 mmol). The mixture was stirred at r.t. overnight, then diluted with aqueous sodium

20 bicarbonate and extracted with ethyl acetate. The organic extracts were washed with brine, dried over MgSO₄ and concentrated to a colorless oil. The product (compound 35) was

purified by silica gel chromatography using methanol/ethyl acetate/ammonium hydroxide as the eluent.

¹H NMR (CDCl₃) δ 7.40-6.95 (m, 13H), 4.20 (s, 4H), 3.42 (s, 2H), 3.25 (s, 3H), 2.32 (s, 6H).

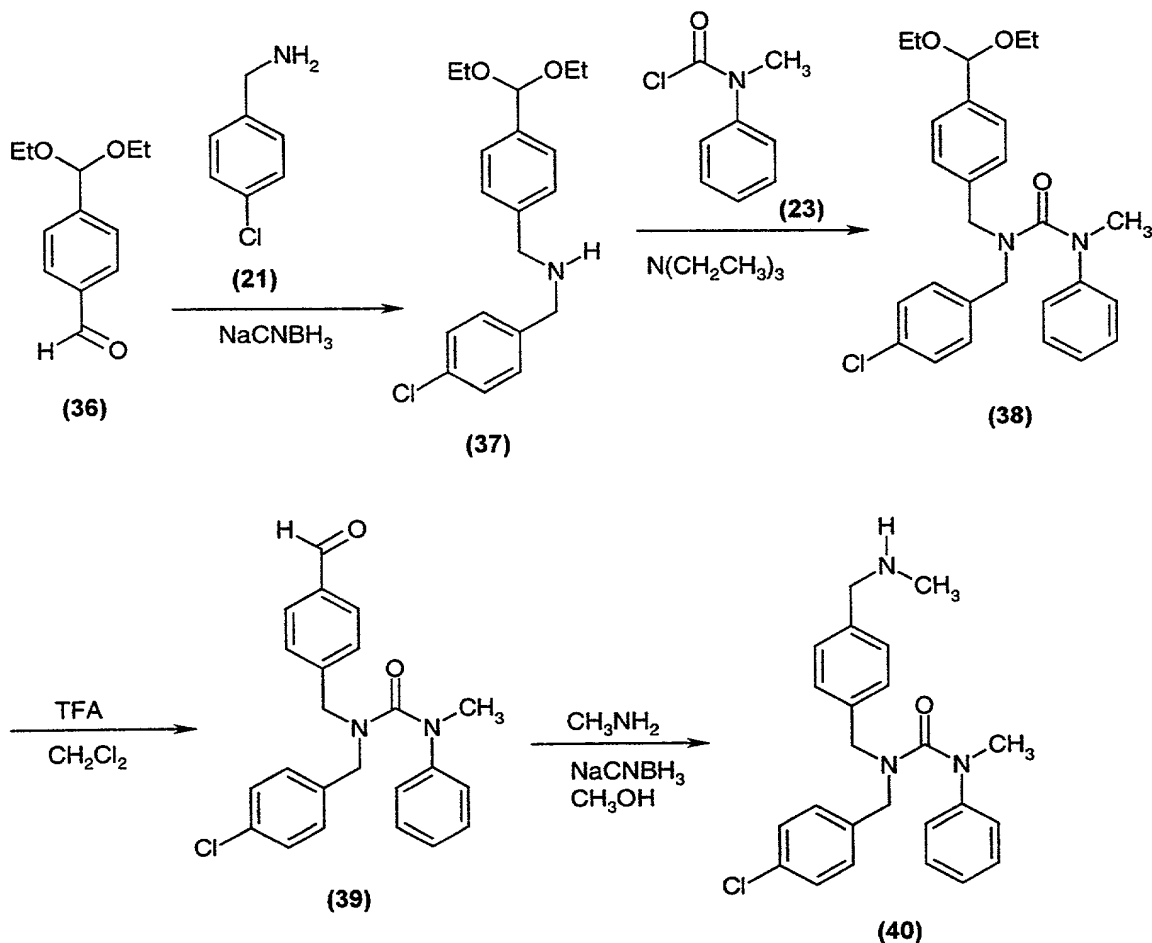
MS: 422. (M+H).

EXAMPLE 14

Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-(N-methyl)-aminomethyl-benzene (Compound 40)

The compound 40 of Example 13 was prepared by following the procedure described in Scheme 6 below.

Scheme 6

**Step 1****Preparation of 1-diethyl acetal-4-N-(4-chlorobenzyl) benzyl amine (compound 37)**

- 5 To a solution of *tere*-phthalaldehyde *mono*-(diethyl acetal) (compound 36) (0.416 g, 2 mmol) and 4-chlorobenzylamine (compound 21) (0.283 g, 2 mmol) in methanol (5 mL, containing 1% glacial acetic acid v/v) was added solid NaCNBH_3 . The reaction mixture was stirred at r.t. overnight. It was diluted with aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over
- 10 MgSO_4 and concentrated to an oil, (compound 37): .61 g (91%). MS: 334.02 (M+H).

Step 2**Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-carboxaldehyde (compound 39)**

5 To a solution of 1-diethyl acetal-4-N-(4-chlorobenzyl) benzyl amine (compound 37) (0.60 g, 1.8 mmol) in dioxane (5 mL) was added triethylamine (0.279 mL, 2 mmol) and N-methyl,N-phenyl carbamoyl chloride (compound 23) (0.336g, 1.98 mmol). The mixture was stirred at r.t. overnight, then diluted with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic extracts were washed with brine, dried over MgSO₄ and
10 concentrated to give (compound 38) : 0.69 g.

The acetal (compound 38) (0.67 g, 1.42 mmol) was dissolved in 50% trifluoroacetic acid/methylene chloride (5 mL) and stirred at r.t. for 3.5 h. The mixture was concentrated to an oily residue which was redissolved in CH₂Cl₂ and washed with sodium bicarbonate,
15 brine, dried over MgSO₄ and concentrated to an oil, (compound 39): 0.504 g.

¹H NMR (CDCl₃) δ 9.80 (s, 1H), 7.72-6.68 (m, 13H), 4.10 (s, 2H), 3.97 (s, 2H), 3.10 (s, 3H).

Step 3**Preparation of 1-N-[(4-chlorobenzyl)-N-(N-methyl-N-phenylcarbamoyl)]-aminomethyl-4-(N-methyl)-aminomethyl-benzene (compound 40)**

To a methanolic solution (5 mL) of compound 39 (0.50 g, 1.28 mmol) was added a solution of 2M methylamine in methanol (0.7 mL, 1.40 mmol), and glacial acetic acid
25 (0.05 mL). Solid NaCNBH₃ (0.08 g, 1.28 mmol) was then added and the mixture was stirred at r.t. overnight. It was diluted with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic extracts were washed with brine, dried and concentrated. The product (compound 40) was purified by silica gel chromatography, using a mixture of methanol/methylene chloride/ammonium hydroxide as the eluent.

$^1\text{H NMR (CDCl}_3)$ δ 7.40-6.95 (m, 13H), 4.19 (s, 2H), 4.16 (s, 2H), 3.82 (s, 2H), 3.19 (s, 3H), 2.46 (s, 3H).

MS: 408.03. (M+H).

5 Pharmaceutical compositions

The novel compounds according to the present invention may be administered orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the
10 joints.

A preferred route of administration is orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and
15 weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert,
20 pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring
agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents;
25 it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided
active component. In tablets, the active component is mixed with the carrier having the
necessary binding properties in suitable proportions and compacted in the shape and size
30 desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient
 5 sized molds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

10 Pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide,
 15 hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoate, triethiodide, benzathine, chlorprocaine, choline, diethanolamine,
 20 ethylenediamine, meglumine, procaine, aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc.

Preferred pharmaceutically acceptable salts are the hydrochlorides, trifluoroacetates and bitartrates.

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it.

5 Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

10 Liquid from compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

15 Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other
20 suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical compositions is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing
25 discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

BIOLOGICAL EVALUATION

A) IN VITRO MODEL

Cell culture

5

Human 293S cells expressing cloned human μ , δ , and κ receptors and neomycin resistance were grown in suspension at 37°C and 5% CO₂ in shaker flasks containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 µg/ml geneticin.

10

Membrane preparation

Cells were pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension was spun at 1000g (max) for 10 min at 4°C. The supernatant was saved on ice and the pellets resuspended and spun as before. The supernatants from both spins were combined and spun at 46,000 g(max) for 30 min. The pellets were resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets were resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes were frozen in dry ice/ethanol and stored at -70°C until use. The protein concentrations were determined by a modified Lowry assay with SDS.

Binding assays

25 Membranes were thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM MgCl₂, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which was stored at 4°C after filtration through a 0.22 m filter, and to which had been freshly added 5 µg/ml aprotinin, 10 µM bestatin, 10 µM diprotin A, no DTT). Aliquots of 100 µl (for µg protein, see Table 1) were added to iced 12x75 mm
30 polypropylene tubes containing 100 µl of the appropriate radioligand (see Table 1) and

100 μ l of test peptides at various concentrations. Total (TB) and nonspecific (NS) binding were determined in the absence and presence of 10 μ M naloxone respectively. The tubes were vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM MgCl₂) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters was measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which were washed with 3 x 1 ml wash buffer, and dried in an oven at 55°C for 2h. The filter plates were counted in a TopCount (Packard) after adding 50 μ l MS-20 scintillation fluid/well.

Data analysis

15 The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test peptides was expressed as percentage of control SB. Values of IC₅₀ and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prussoff equation. Mean \pm S.E.M. values of IC₅₀, K_i and n_H were reported for ligands tested in at least three displacement curves.

Receptor saturation experiments

Radioligand K_D values were determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated K_D (up to 10 times if amounts of radioligand required are feasible). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of K_D and B_{max} from individual experiments were obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

10 B) BIOLOGICAL MODEL (IN VIVO MODEL)

FREUND'S COMPLETE ADJUVANT (FCA), AND SCIATIC NERVE CUFF INDUCED MECHANO-ALLODYNIA IN RAT

Animals

15 Male Sprague-Dawley rats (Charles River, St-Constant, Canada) weighing 175-200g at the time of surgery were used. They were housed in groups of three in rooms thermostatically maintained at 20° C with a 12:12 hr light/dark cycle, and with free access to food and water. After arrival, the animals were allowed to acclimatize for at least 2 days before surgery. The experiments were approved by the appropriate Medical Ethical Committee
20 for animal studies.

EXPERIMENTAL PROCEDURE

FREUND'S COMPLETE ADJUVANT

25 The rats were first anesthetized in a Halothane chamber after which 10µl of FCA was injected s.c. into the dorsal region of the left foot, between the second and third external digits. The animals were then allowed to recover from anesthesia under observation in their home cage.

SCIATIC NERVE CUFF

The animals were prepared according to the method described by Mosconi and Kruger (1996). Rats were anesthetized with a mixture of Ketamine / Xylazine i.p. (2ml/kg) and placed on their right side and an incision made over, and along the axis of, the lateral
5 aspect of the left femur. The muscles of the upper quadriceps were teased apart to reveal the sciatic nerve on which a plastic cuff (PE-60 tubing, 2mm long) was placed around. The wound was then closed in two layers with 3-0 vicryl and silk sutures.

DETERMINATION OF MECHANO-ALLODYNIA USING VON FREY TESTING

10 Testing was performed between 08:00 and 16:00h using the method described by Chaplan et al. (1994). Rats were placed in Plexiglas cages on top of a wire mesh bottom which allowed access to the paw, and were left to habituate for 10-15 min. The area tested was the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw was touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69,
15 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair was applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Ambulation was
20 considered an ambiguous response, and in such cases the stimulus was repeated.

TESTING PROTOCOL

The animals were tested on postoperative day 1 for the FCA-treated group and on post-operative day 7 for the Sciatic Nerve Cuff group. The 50% withdrawal threshold was
25 determined using the up-down method of Dixon (1980). Testing was started with the 2.04 g hair, in the middle of the series. Stimuli were always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. Optimal threshold calculation by this method

requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses began when the first change in response occurred, e.g. the threshold was first crossed. In cases where thresholds fell outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) were respectively assigned. The resulting pattern of positive and negative responses was tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold was interpolated using the formula:

$$50\% \text{ g threshold} = 10^{(X_f + k\delta)} / 10,000$$

where X_f = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

Von Frey thresholds were converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation was used to compute % MPE:

$$\% \text{ MPE} = \frac{\text{Drug treated threshold (g)} - \text{allodynia threshold (g)}}{\text{Control threshold (g)} - \text{allodynia threshold (g)}} \times 100$$

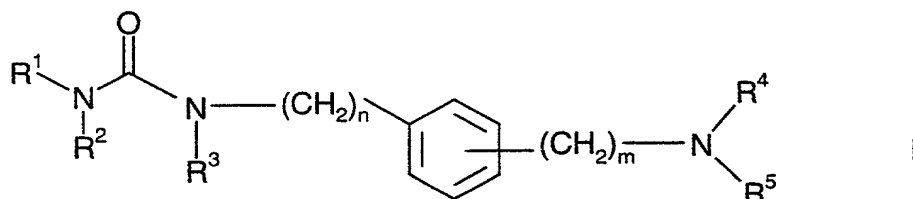
ADMINISTRATION OF TEST SUBSTANCE

Rats were injected (subcutaneously, intraperitoneally, or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varied depending upon the nature of the test compound.

CLAIMS

1. A compound according to formula I

5



wherein

m and n is each and independently an integer of from 1-3, and one or more of the hydrogens in such an alkylene-chain may optionally be substituted by anyone of

10 C₁ - C₆ alkyl, C₁ - C₆ alkoxy, or hydroxy; *or*

one or more of the methylene groups may optionally be substituted by a heteroatom such as O, N or S;

15 R¹ is selected from hydrogen, a branched or straight C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₈ cycloalkyl, C₄-C₈(alkyl-cycloalkyl) wherein the alkyl is C₁-C₂ alkyl and the cycloalkyl is C₃-C₆ cycloalkyl;

R² is selected from any of

20

(i) hydrogen;

(ii) a straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

25 (iii) -[(CH₂)_q- aryl];

(iv) $-(\text{CH}_2)_r\text{-heteroaryl}$] where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;

and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below; and wherein q and r is each and
5 independently an integer of from 0 to 3;

(v) $\text{C}_3\text{-C}_{10}$ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;

10 and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi) $\text{C}_6\text{-C}_{10}$ aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O
15 and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted
20 by 1 or 2 substituents Y wherein each Y is as defined below;

or

R^1 and R^2 may optionally form a heterocyclic ring;

25 R^3 is selected from anyone of

(i) hydrogen;

(ii) a straight or branched $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl or $\text{C}_2\text{-C}_6$ alkynyl;

(iii) $-\text{[(CH}_2\text{)}_q\text{-aryl]}$ wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is
5 as defined below;

(iv) heteroaryl-(C₅ - C₁₀ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as
10 defined below;

(v) C₃-C₁₀ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally
15 and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi) $-\text{[(C}_3\text{-C}_6\text{ cycloalkyl)-(CH}_2\text{)}_q\text{]}$ wherein q is an integer of from 1 to 3;

20 R^4 is selected from

(i) hydrogen;

(ii) a straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

25

(iii) $-\text{[(CH}_2\text{)}_q\text{-aryl]}$ wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl

may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(iv) heteoaryl-(C₅ - C₁₀ alkyl), where the heteoaryl has from 5 to 10 atoms and the
5 heteoatom being selected from any of S, N and O, and wherein the aryl and heteoaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(v) C₃-C₁₀ cycloalkyl, optionally comprising one or more unsaturations and optionally
10 susbtituted by one or more heteoaryl(s) where the heteoaryl has from 5 to 10 atoms and the heteoatom being selected from any of S, N and O; and wherein the aryl and heteoaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi) C₆-C₁₀ aryl, optionally and independently substituted by one or more heteoaryl(s)
15 having from 5 to 10 atoms and the heteoatom(s) being selected from any of S, N and O and wherein the heteoaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

20 (vii) heteoaryl having from 5 to 10 atoms and the heteoatom being selected from any of S, N and O; wherein the aryl and heteoaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

25 R⁵ is selected from anyone of

(i) hydrogen;

(ii) a straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

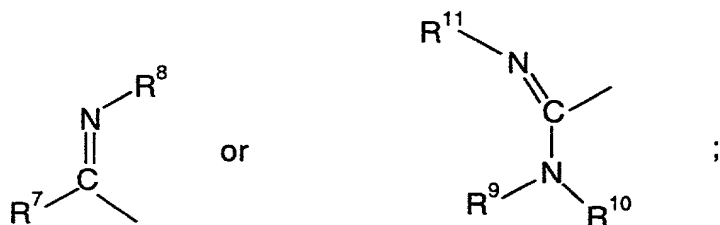
30

(iii) $-(\text{CH}_2)_q\text{-aryl}$ wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(iv) heteroaryl-($\text{C}_5 - \text{C}_{10}$ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(v) $\text{C}_3\text{-C}_{10}$ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi)



20

wherein

$\text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}$ and R^{11} is each and independently selected from

25

(a) hydrogen;

(b) a straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

(c) -[(CH₂)_q-aryl] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(d) heteoaryl-(C₅ - C₁₀ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(e) C₃-C₁₀ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(f) C₆-C₁₀ aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

or

R⁴ and R⁵ may optionally form a heterocyclic ring;

Y is each and independently selected from any of hydrogen, CH₃; —(CH₂)_{p1}CF₃; halogen; C₁-C₃ alkoxy; hydroxy; -NO₂; -OCF₃; —CONR^aR^b; —COOR^a; —COR^a; —(CH₂)_{p2}NR^aR^b; —(CH₂)_{p3}CH₃, (CH₂)_{p4}SOR^aR^b; —(CH₂)_{p5}SO₂R^a; —(CH₂)_{p6}SO₂NR^a; C₄-C₈(alkyl-cycloalkyl) wherein alkyl is C₁-C₂ alkyl and cycloalkyl is C₃-C₆ cycloalkyl; 1 or 2 heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O; and oxides such as N-oxides or sulfoxides; and wherein

R^a and R^b is each and independently selected from hydrogen, a branched or straight C₁-C₆ alkyl, C₁-C₆ alkenyl, C₃-C₈ cycloalkyl; and wherein p¹, p², p³, p⁴, p⁵ and p⁶ is each and independently 0, 1 or 2;

as well as pharmaceutically acceptable salts, isomers, hydrates, isoforms and prodrugs thereof.

2. A compound according to formula I of claim 1, wherein m=n=1

R¹ is selected from

- (i) hydrogen;
- (ii) a branched or straight C₁-C₆ alkyl; or
- (iii) C₃-C₈ cycloalkyl;

R² is selected from any of

(i) hydrogen;

(ii) a straight or branched C₁-C₆ alkyl;

5

(iii) -[(CH₂)_q- aryl];

(iv) -[(CH₂)_r- heteroaryl] where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;

and wherein the aryl and heteroaryl may optionally and independently be substituted by

10 1 or 2 substituents Y where each Y is as defined in claim 1; and wherein q and r is each and independently an integer of from 0 to 3;

(v) C₃-C₆ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;

15

and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(vi) C₆-C₁₀ aryl, optionally and independently be substituted by 1 or 2 substituents Y

20

wherein each Y is as defined in claim 1;

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted

25

by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

or

R¹ and R² may optionally form a heterocyclic ring;

R³ is selected from anyone of

- (i) hydrogen;
- 5 (ii) a straight or branched C₁-C₆ alkyl;
- (iii) -[(CH₂)_q-aryl] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl
- 10 may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;
- (iv) heteroaryl-(C₅ - C₁₀ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may
- 15 optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;
- (v) C₃-C₁₀ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom
- 20 being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;
- (vi) -[(C₃-C₆ cycloalkyl)-(CH₂)_q] wherein q is an integer of from 1 to 3;

25

R⁴ is selected from

- (i) hydrogen;
- (ii) a straight or branched C₁-C₆ alkyl;

(iii) $-(\text{CH}_2)_q\text{-aryl}$] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl
5 may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iv) heteroaryl-($\text{C}_5 - \text{C}_{10}$ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may
10 optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(v) $\text{C}_6\text{-C}_{10}$ aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O
15 and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

R^5 is selected from anyone of

20

(i) hydrogen;

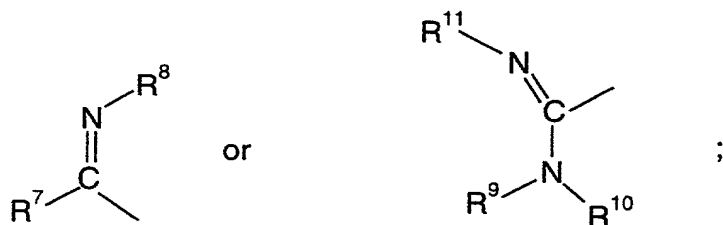
(ii) a straight or branched $\text{C}_1\text{-C}_6$ alkyl;

(iii) $-(\text{CH}_2)_q\text{-aryl}$ wherein q is 0 or 1, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in
 5 claim 1;

(iv) heteroaryl-($\text{C}_5 - \text{C}_{10}$ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as
 10 defined in claim 1;

(v) $\text{C}_3\text{-C}_6$ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally
 15 and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(vi)



20

wherein

R^7 , R^8 , R^9 , R^{10} and R^{11} is each and independently selected from

25

(a) hydrogen;

(b) a straight or branched $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_2\text{-C}_6$ alkenyl;

(c) $-(\text{CH}_2)_q\text{-aryl}$] wherein q is an integer of from 0 to 3, and wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(d) heteoaryl-($\text{C}_5 - \text{C}_{10}$ alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(e) $\text{C}_3\text{-C}_{10}$ cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(f) $\text{C}_6\text{-C}_{10}$ aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

or

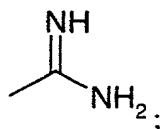
R^4 and R^5 may form a heterocyclic ring which may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1.

R⁵ is selected from

(i) hydrogen;

(ii) methyl; *or*

5 (iii)

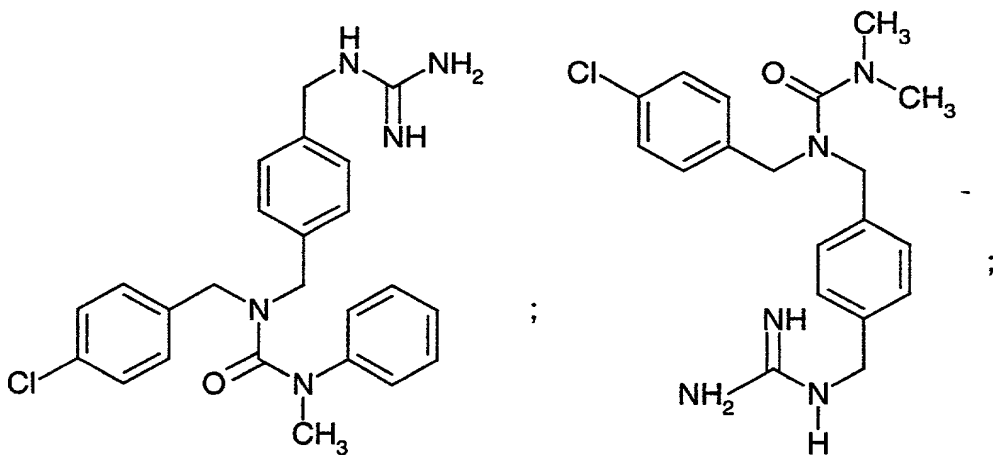


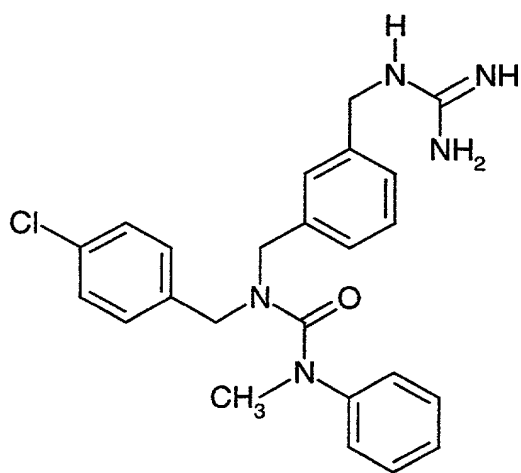
or

10 R⁴ and R⁵ together form a heterocyclic ring, optionally substituted by 1 or 2 substituents Y, where Y is as defined in claim 1.

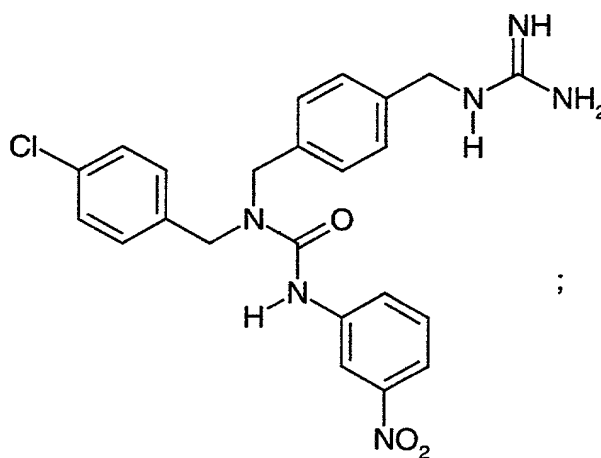
4. A compound according to claim 1, which compound is anyone selected from

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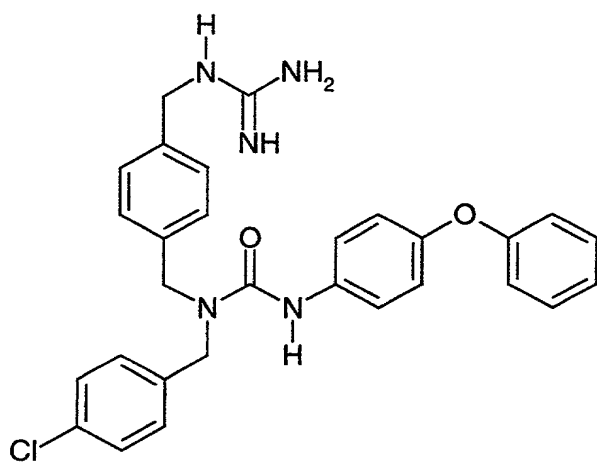




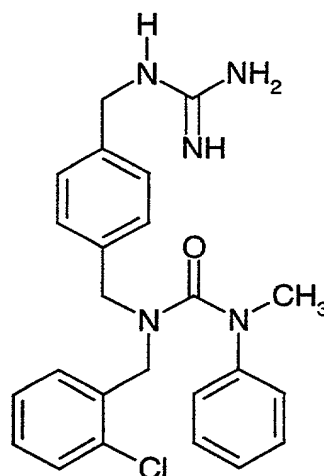
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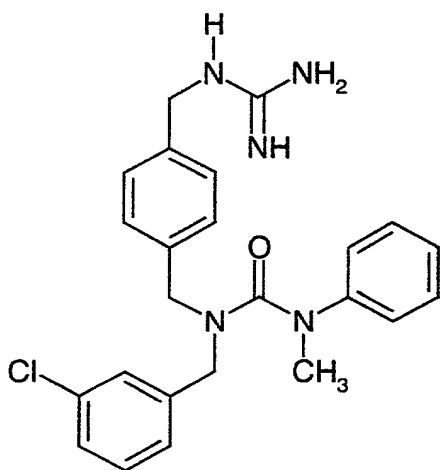
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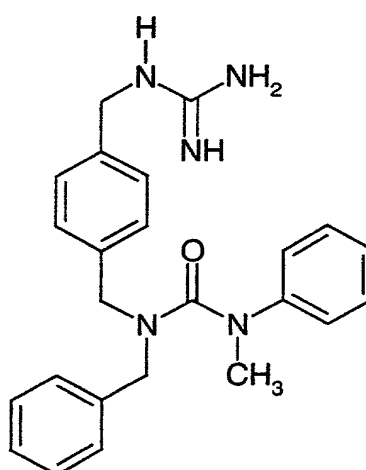
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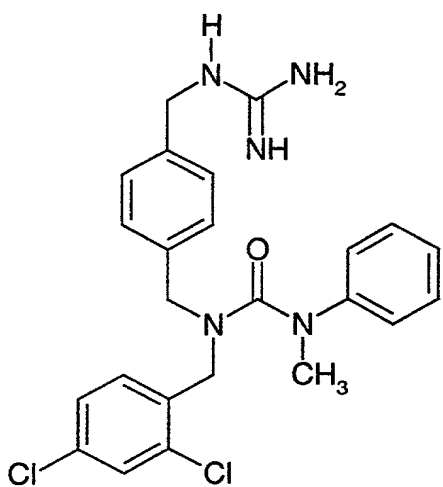
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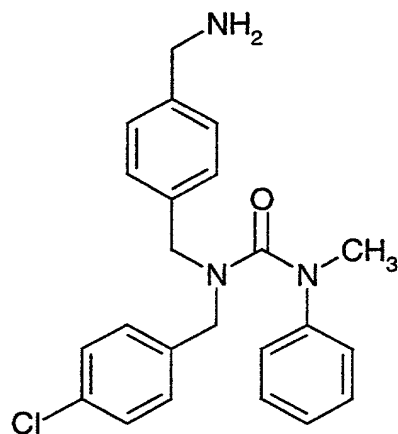
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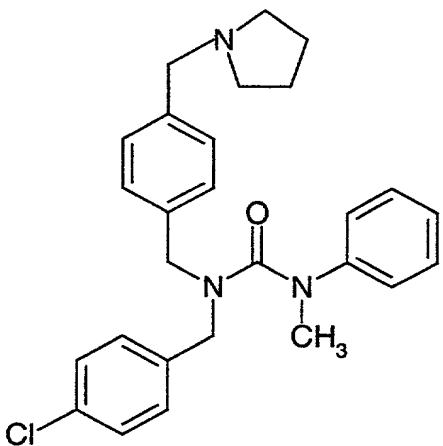
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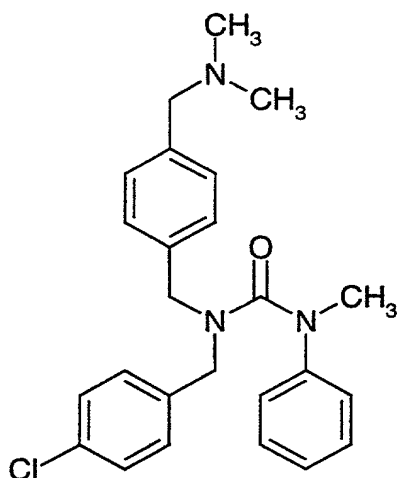
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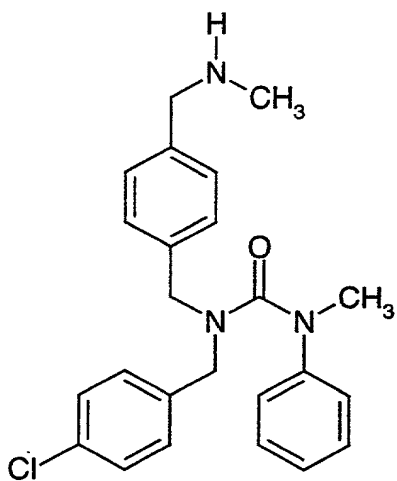


;



; and

5



5. A compound according to any of the preceding claims, in form of its hydrochloride, sulfate, tartrate or citrate salts.
- 5 6. A compound according to any of claims 1-5 for use in therapy.
7. A compound according to claim 6, wherein the therapy is pain management.
8. A compound according to claim 6, wherein the therapy is directed towards
10 gastrointestinal disorders.
9. A compound according to claim 6, wherein the therapy is directed towards spinal injuries.
- 15 10. A compound according to claim 6, wherein the therapy is directed to disorders of the sympathetic nervous system.
11. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of pain.
- 20 12. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of gastrointestinal disorders.
13. Use of a compound according to formula I of claim 1 for the manufacture of a
25 medicament for use in the treatment of spinal injuries.
14. A compound according to any of claims 1-10, further characterised in that it is isotopically labelled.
- 30 15. Use of a compound according to claim 14 as a diagnostic agent.

16. An isotopically labelled compound of the formula I of claim 1.

17. A diagnostic agent comprising a compound of the formula I of claim 1.

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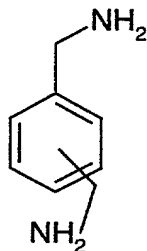
18. A pharmaceutical composition comprising a compound of the formula I according to claim 1 as an active ingredient, together with a pharmacologically and pharmaceutically acceptable carrier.

10 19. A process for the preparation of a compound of the formula I according to claim 1, whereby

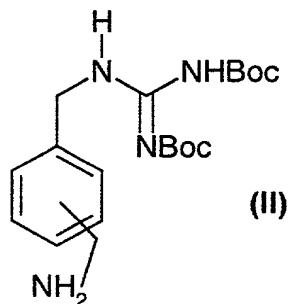
A)

(i) bis-amino xylylene of the formula

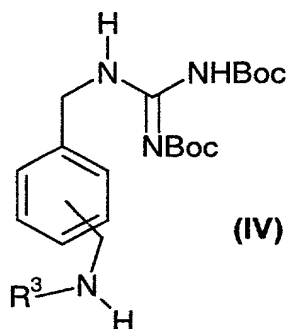
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is converted into mono-(diBoc)-guanidinomethyl of the formula (II)

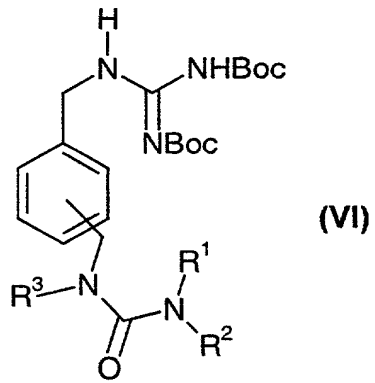


- 5 which thereafter is reacted with an aldehyde, providing a secondary amine of the general formula IV

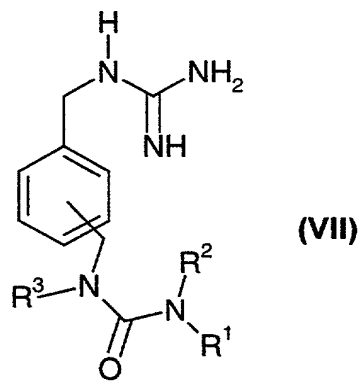


- 10 wherein R³ is as defined in formula I of claim 1;

(ii) compound IV is subjected to an urea formation, providing a compound of the formula (VI)



which finally is deprotected, providing a compound of the general formula VII



5 . wherein

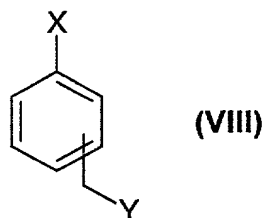
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R^1 , R^2 and R^3 are as defined in formula I of claim 1; *or*

B)

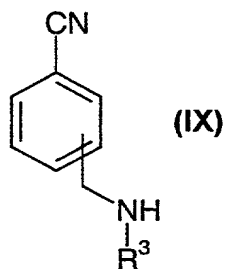
(i) a compound of the formula (VIII)

5



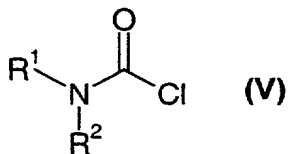
wherein X is CN and Y is CHO, is subjected to a reductive amination using a primary amine R^3NH_2 wherein R^3 is as defined in formula I of claim 1, providing a compound of the formula (IX)

10

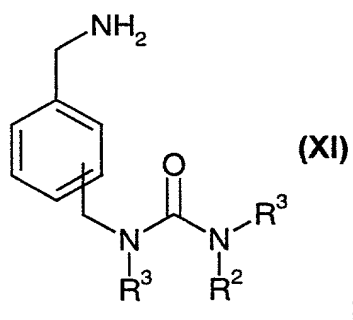


wherein R^3 is as defined in formula I of claim 1, which thereafter is subjected to an urea reaction by using a chloroformate of the formula (V)

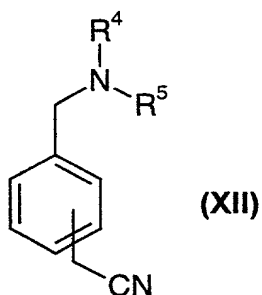
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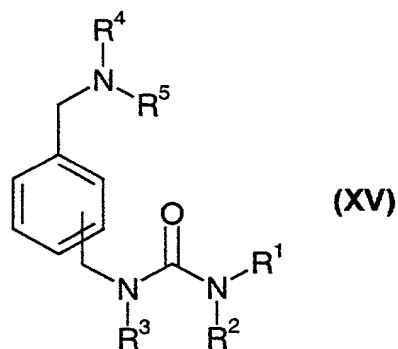
which finally is reduced, providing a compound of the formula (XI)



- (ii) compound (VIII) wherein X is CH₂Br and Y is CN, is reacted with an amine R⁴R⁵NH wherein R⁴ and R⁵ are as defined in formula I of claim 1, providing a compound of the formula (XII)



- which is reduced and reacted with an aldehyde R³CHO wherein R³ is as defined in formula I of claim 1, and finally subjected to an urea action with a chloroformate (V) as in step (i), providing a compound of the formula (XV)



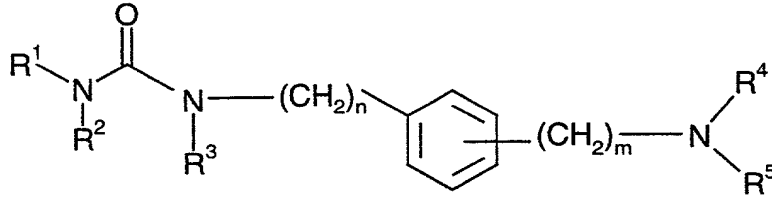
- wherein R¹, R², R³, R⁴ and R⁵ are as defined in formula I of claim 1.

20. A method for the treatment of pain, whereby an effective amount of a compound of the formula I according to claim 1 is administered to a subject in need of pain management.
- 5
21. A method for the treatment of gastrointestinal disorders, whereby an effective amount of a compound of the formula I according to claim 1, is administered to a subject suffering from said gastrointestinal disorder.
- 10
22. A method for the treatment of spinal injuries, whereby an effective amount of a compound of the formula I according to claim 1, is administered to a subject suffering from said spinal injury.

Abstract

Compounds of general formula I

5



I

are disclosed and claimed in the present application, as well as their pharmaceutically acceptable salts, pharmaceutical compositions comprising the novel compounds and their use in therapy, in particular in the management of pain.

10

09/555575
422 Rec'd PCT/PTO 01 JUN 2000

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Delorme, et al. Group Art Unit: to be assigned
Appln. No. to be assigned/ Examiner: to be assigned
Filing Date: June 1, 2000 Atty Dkt PMS 81823/268623
M# / Client Ref.
Title: Novel Compounds Useful Date: June 1, 2000
in Pain Management

* * * * *

CHANGE OF ADDRESS NOTICE

Asst. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Effective immediately, please change the correspondence address to:

Pillsbury Madison & Sutro LLP
Intellectual Property Group
1100 New York Avenue, NW
Ninth Floor
Washington, DC 20005-3918

Our general telephone number is: (202) 861-3000.

Respectfully submitted,

Pillsbury Madison & Sutro LLP
Intellectual Property Group

By Michael A. Sanzo
Atty: Michael A. Sanzo
Reg. No. 36912
Tel.: (202) 861-3020
Fax.: (202) 822-0944

Atty/Sec: MAS/CJT

DECLARATION (37 C.F.R. § 1.63) AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

NOVEL COMPOUNDS USEFUL IN PAIN MANAGEMENT

the specification of which

(check one)

is attached hereto.

was filed on 16 June 1999 as PCT International Application No. SE99/01075 and was amended under PCT Article 19 on _____, (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any United States provisional application(s) or foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

<u>Application Serial No.</u>	<u>Country</u>	<u>Filing Date (Day/Month/Year)</u>	<u>Priority Claimed (Yes/No)</u>
9802209-8	Sweden	22 June 1998	Yes

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status (Patented, Pending, Abandoned)</u>
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

23

I hereby appoint Steven R. Borgman, Reg. No. 33,160; Barry Bumgardner, Reg. No. 38,397; W. Scott Brown, Reg. No. 32,968; Brian K. Buss, Reg. No. 42,375; Tim S. Corder, Reg. No. 38,414; Tracey Davies, Reg. No. 44,644; Andrew F. DiNovo, Reg. No. 40,115; G. Harvey Dunn, III, Reg. No. 31,102; Barry E. Engel, Reg. No. 37,127; Adam Floyd, Reg. No. 39,192; Stuart J. Ford, Reg. No. 37,486; Sunny Kalara, Reg. No. 43,702; William L. LaFuze, Reg. No. 27,205; Gerald D. Malpass, Reg. No. 40,079; J. Clark Martin, Reg. No. 26,198; Peter E. Mims, Reg. No. 32,429; Stephen J. Moloney, Reg. No. 44,947; Minh-Hien Nguyen, Reg. No. 37,294; Gregory L. Porter, Reg. No. 40,131; W. Ronald Robins, Reg. No. 26,222; Michael A. Sanzo, Reg. No. 36,912; Willem G. Schuurman, Reg. No. 29,998; and Karen Tucker White, Reg. No. 34,267, all registered to practice before the Patent and Trademark Office, as my attorneys with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith and request that all correspondence and telephone communications be directed to the following person(s) at the mailing address and telephone number hereafter given:

Name:	Michael A. Sanzo
Registration No.:	36,912
Address:	Vinson & Elkins L.L.P. 2300 First City Tower 1001 Fannin Houston, TX 77002-6760
Telephone No.:	(202) 639-6585

001030-6288660

DECLARATION (37 C.F.R. § 1.63) AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

NOVEL COMPOUNDS USEFUL IN PAIN MANAGEMENT

the specification of which

(check one)

is attached hereto.

was filed on 16 June 1999 as PCT International Application No. SE99/01075 and was amended under PCT Article 19 on _____, (if applicable).

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<u>Application Serial No.</u>	<u>Country</u>	<u>Filing Date (Day/Month/Year)</u>	<u>Priority Claimed (Yes/No)</u>
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<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status (Patented, Pending, Abandoned)</u>
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint Steven R. Borgman, Reg. No. 33,160; Barry Bumgardner, Reg. No. 38,397; W. Scott Brown, Reg. No. 32,968; Brian K. Buss, Reg. No. 42,375; Tim S. Corder, Reg. No. 38,414; Tracey Davies, Reg. No. 44,644; Andrew F. DiNovo, Reg. No. 40,115; G. Harvey Dunn, III, Reg. No. 31,102; Barry E. Engel, Reg. No. 37,127; Adam Floyd, Reg. No. 39,192; Stuart J. Ford, Reg. No. 37,486; Sunny Kalara, Reg. No. 43,702; William L. LaFuze, Reg. No. 27,205; Gerald D. Malpass, Reg. No. 40,079; J. Clark Martin, Reg. No. 26,198; Peter E. Mims, Reg. No. 32,429; Stephen J. Moloney, Reg. No. 44,947; Minh-Hien Nguyen, Reg. No. 37,294; Gregory L. Porter, Reg. No. 40,131; W. Ronald Robins, Reg. No. 26,222; Michael A. Sanzo, Reg. No. 36,912; Willem G. Schuurman, Reg. No. 29,998; and Karen Tucker White, Reg. No. 34,267, all registered to practice before the Patent and Trademark Office, as my attorneys with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith and request that all correspondence and telephone communications be directed to the following person(s) at the mailing address and telephone number hereafter given:

Name:	Michael A. Sanzo
Registration No.:	36,912
Address:	Vinson & Elkins L.L.P. 2300 First City Tower 1001 Fannin Houston, TX 77002-6760
Telephone No.:	(202) 639-6585

UNITED STATES
DEPARTMENT OF COMMERCE

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Inventor's Signature *D. Delorme* Date March 9, 2000

Full name of sole inventor: Daniel Delorme
 Residence Address: Quebec, Canada
 Citizenship: Canadian CHX
 Post Office Address: MethylGene, Inc., 7220 Frederick-Banting, Montreal, Quebec H4S 2A1, Canada

Inventor's Signature _____ Date _____

Full name of sole inventor: Vlad Gregor
 Residence Address: San Diego, California, USA
 Citizenship: United States
 Post Office Address: 12283 Carmel Vista Road #219, San Diego, California 92130, USA

Inventor's Signature *E. Roberts* Date 16th March 2000

Full name of sole inventor: Edward Roberts
 Residence Address: Solothurn, Switzerland CHX
 Citizenship: British
 Post Office Address: Höhenweg 12, CH-4112 Flüh, Solothurn, Switzerland

Inventor's Signature _____ Date _____

Full name of sole inventor: Eric Sun
 Residence Address: San Diego, California, USA
 Citizenship: United States
 Post Office Address: Alanex Corp., 3550 General Atomics Ct., San Diego, California 92121, USA

000000000000000000000000000000000000

INVENTOR'S SIGNATURE _____ Date _____

Full name of sole inventor: Daniel Delorme
Residence Address: Quebec, Canada
Citizenship: Canadian
Post Office Address: MethylGene, Inc., 7220 Frederick-Banting, Montreal, Quebec H4S 2A1, Canada

2-00

INVENTOR'S SIGNATURE *Vlad Gregor* Date *April 13, 2000*

Full name of sole inventor: Vlad Gregor
Residence Address: San Diego, California, USA CA.
Citizenship: United States
Post Office Address: 12283 Carmel Vista Road #219, San Diego, California 92130, USA

INVENTOR'S SIGNATURE _____ Date _____

Full name of sole inventor: Edward Roberts
Residence Address: Solothurn, Switzerland
Citizenship: British
Post Office Address: Höhenweg 12, CH-4112 Flüh, Solothurn, Switzerland

001050-00

INVENTOR'S SIGNATURE *Eric Sun* Date *2-28-2000*

Full name of sole inventor: Eric Sun
Residence Address: San Diego, California, USA CA.
Citizenship: United States
Post Office Address: Alanex Corp., 3550 General Atomics Ct., San Diego, California 92121, USA